PCT/05-49678.

Industria y Comercio

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Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

05-49678

21. **EXPEDIENTE No.** _____

54. **TÍTULO** HETEROCICLOS QUE CONTIENEN NITROGENO, BICICLICOS FUSIONADOS

51. **CLASIFICACIÓN INTERNACIONAL** A61K31/505; A61K31/539 A61P35/00.

71. **SOLICITANTE** JAPAN TOBACCO INC.

DOMICILIO Minato-Ku, Japon

74. **APODERADO** DILIA RODRIGUEZ D'ALEMAN

22. **BOGOTÁ, D. C.,** MAYO 23 2003

(FORMA P-10)

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PETITORIO

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Dependencia: 200 DIVISION DE NUEVAS SOLICITUDES

Industria y Comercio
SUPERINTENDENCIA

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL 22-06-05

1) SOLICITUD DE:

☒ Patente de invención ☐ Patente de Modelo de Utilidad

☐ Capitulo I. ☒ Capitulo II.

2) SOLICITANTE (71)	**Nombre: JAPAN TOBACCO INC.** **Dirección: 2-1. Toranomon 2-chome, Minato-ku, Tokio 105-8422, Japón** **Nacionalidad o domicilio: Minato-ku, Japón** **Lugar de constitución: Japón**	**IDENTIFICACIÓN** **C.C.** ☐ **NIT:** ☐ **C.E.** ☐ **OTRO** ☐ **Cual** _____ **NÚMERO** _____
	Teléfono: **Fax:** **E. Mail:**	
3) REPRESENTANTE O APODERADO	Nombre: DILIA MARÍA RODRÍGUEZ D´ALEMAN Dirección: Carrera 11 N°. 86-53 Piso 6 Bogotá D.C. Teléfono: 6181088 Fax: 6350824 E. Mail: info@clarkemodet.com.co	**IDENTIFICACIÓN** **C.C.** ☒ **NIT:** ☐ **C.E.** ☐ **OTRO** ☐ **NÚMERO: 41.654.882** **TP: 20824 CSJ**
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Solicitud Internacional No. PCT/US2003/037574 Fecha: NOV. 21, 2003

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6)Título (54) HETEROCICLOS QUE CONTIENEN NITRÓGENO, BICICLICOS, FUSIONADOS

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9) Comprobante de pago N°. 05-37,661 Fecha: Mayo 20, 2005

Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta pagina

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10) ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud
- [ ] Comprobante de pago por reivindicación de prioridad
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona Jurídica
- [ ] Poderes, si fuera el caso
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [x] Copia de la solicitud Internacional. (Resumen, descripción, reivindicación, Dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicación, Dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [ ] Arte final 12 x 12 y 6 x 6 cm
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud.
- [x] Otros:

1. Solicitud PCT

11) FIGURA CARACTERÍSTICA:

12) Solicitud concesión de la patente,

NOMBRE: DILIA RODRÍGUEZ D´ALEMAN

FIRMA:

C.C. 41.654.882 de Bogota TP 20824 CSJ

Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta pagina

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FECHA : MAYO 20 DE 2005

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CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO POPULAR	050-00110-6	41478402	20/05/2005	4,276,000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	443,000.00
		TOTAL : $	443,000.00

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: FUSED BICYCLIC NITROGEN-CONTAINING HETEROCYCLES

(57) Abstract: Compounds, pharmaceutical compositions and methods that are useful in the treatment or prevention of metabolic and cell proliferative diseases or conditions are provided herein. In particular, the invention provides compounds which modulate the activity of proteins involved in lipid metabolism and cell proliferation.

WO 2004/047755 A2

Fused Bicyclic Nitrogen-Containing Heterocycles

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of US Provisional Application Serial No. 60/428,600, filed November 22, 2002, the content of which is incorporated herein by reference.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] NOT APPLICABLE

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK.

[0003] NOT APPLICABLE

BACKGROUND OF THE INVENTION

[0004] Triglycerides represent the major form of energy stored in eukaryotes. Disorders or imbalances in triglyceride metabolism are implicated in the pathogenesis of and increased risk for obesity, insulin resistance syndrome and type II diabetes, nonalcoholic fatty liver disease and coronary heart disease (*see*, Lewis, *et al*, *Endocrine Reviews* (2002) 23:201 and Malloy and Kane, *Adv Intern Med* (2001) 47:111). Additionally, hypertriglyceridemia is often an adverse consequence of cancer therapy (*see*, Bast, *et al*. *Cancer Medicine*, 5th Ed., (2000) B.C. Decker, Hamilton, Ontario, CA).

[0005] A key enzyme in the synthesis of triglycerides is acyl CoA:diacylglycerol acyltransferase, or DGAT. DGAT is a microsomal enzyme that is widely expressed in mammalian tissues and that catalyzes the joining of 1,2-diacylglycerol and fatty acyl CoA to form triglycerides at the endoplasmic reticulum (*reviewed in* Chen and Farese, *Trends Cardiovasc Med* (2000) 10:188 and Farese, *et al*, *Curr Opin Lipidol* (2000) 11:229). It was originally thought that DGAT uniquely controlled the catalysis of the final step of acylation of diacylglycerol to triglyceride in the two major pathways for triglyceride synthesis, the

glycerol phosphate and monoacylglycerol pathways. Because triglycerides are considered essential for survival, and their synthesis was thought to occur through a single mechanism, inhibition of triglyceride synthesis through inhibiting the activity of DGAT has been largely unexplored.

[0006] Genes encoding mouse DGAT1 and the related human homologs ARGP1 and ARGP2 now have been cloned and characterized (Cases, *et al*, *Proc Natl Acad Sci* (1998) 95:13018; Oelkers, *et al*, *J Biol Chem* (1998) 273:26765). The gene for mouse DGAT1 has been used to create DGAT knock-out mice to better elucidate the function of the DGAT gene. Unexpectedly, mice unable to express a functional DGAT enzyme (*Dgat-/-* mice) are viable and still able to synthesize triglycerides, indicating that multiple catalytic mechanisms contribute to triglyceride synthesis (Smith, *et al*, *Nature Genetics* (2000) 25:87). Other enzymes that catalyze triglyceride synthesis, for example, DGAT2 and diacylglycerol transacylase, also have been identified (Buhman, *J. Biol Chem*, *supra* and Cases, *et al*, *J Biol Chem* (2001) 276:38870).

[0007] Significantly, *Dgat-/-* mice are resistant to diet-induced obesity and remain lean. Even when fed a high fat diet (21% fat) *Dgat-/-* mice maintain weights comparable to mice fed a regular diet (4% fat) and have lower total body triglyceride levels. The obesity resistance in *Dgat-/-* mice is not due to deceased caloric intake, but the result of increased energy expenditure and decreased resistance to insulin and leptin (Smith, *et al*, *Nature Genetics*, *supra*; Chen and Farese, *Trends Cardiovasc Med*, *supra*; and Chen, *et al*, *J Clin Invest* (2002) 109:1049). Additionally, *Dgat-/-* mice have reduced rates of triglyceride absorption (Buhman, *et al*, *J Biol Chem* (2002) 277:25474). In addition to improved triglyceride metabolism, *Dgat-/-* mice also have improved glucose metabolism, with lower glucose and insulin levels following a glucose load, in comparison to wild-type mice (Chen and Farese, *Trends Cardiovasc Med*, *supra*).

[0008] The finding that multiple enzymes contribute to catalyzing the synthesis of triglyceride from diacylglycerol is significant, because it presents the opportunity to modulate one catalytic mechanism of this biochemical reaction to achieve therapeutic results in an individual with minimal adverse side effects. Compounds that inhibit the conversion of diacylglycerol to triglyceride, for instance by specifically inhibiting the activity of the human homolog of DGAT1, will find use in lowering corporeal concentrations and absorption of triglycerides to therapeutically counteract the pathogenic effects caused by abnormal

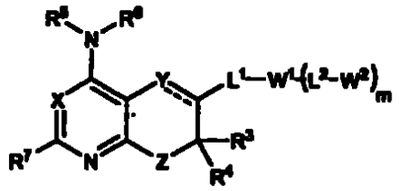
metabolism of triglycerides in obesity, insulin resistance syndrome and overt type II diabetes, congestive heart failure and atherosclerosis, and as a consequence of cancer therapy.

[0009] Because of the ever increasing prevalence of obesity, type II diabetes, heart disease and cancer in societies throughout the world, there is a pressing need in developing new therapies to effectively treat and prevent these diseases. Therefore there is an interest in developing compounds that can potently and specifically modulate a single catalytic mechanism of the enzymatic conversion of diacylglycerol to triglyceride. Of particular promise are compounds that specifically inhibit the catalytic activity of DGAT1 and its other mammalian homologs.

BRIEF SUMMARY OF THE INVENTION

[0010] The present invention provides fused bicyclic nitrogen-containing heterocyclic compounds that are useful for treating or preventing conditions and disorders associated with DGAT in animals, particularly humans.

[0011] In general, the compounds of the present invention are represented by the formula (I):



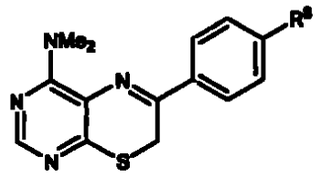
I

or a pharmaceutically acceptable salt, prodrug or stereoisomer thereof, in which the letter X represents $C(R^1)$ or N; the letter Y represents $C(R^1)$, $C(R^2)(R^2)$, N or $N(R^2)$; and the letter Z represents O or S. The symbol L^1 represents a bond, $(C_1\text{-}C_4)$alkylene, $(C_2\text{-}C_4)$alkenylene, O or $N(R^a)C(O)$; and W^1 represents a substituted or unsubstituted member selected from cyclo$(C_3\text{-}C_8)$alkyl, heterocyclo$(C_3\text{-}C_8)$alkyl, aryl and heteroaryl. The subscript m is 0 or 1, indicating the presence (m is 1) or absence (m is 0) of the additional moiety, $L^2\text{-}W^2$. For those embodiments in which m is 1, the symbol L^2 represents a bond, O, $(C_1\text{-}C_4)$alkylene, $(C_2\text{-}C_4)$alkenylene, $(C_1\text{-}C_4)$heteroalkylene or $N(R^a)C(O)$; and the symbol W^2 represents a substituted or unsubstituted member selected from cyclo$(C_3\text{-}C_8)$alkyl, heterocyclo$(C_3\text{-}C_8)$alkyl, aryl and heteroaryl.

[0012] The remaining substituents, R^1 through R^7 and R^a and R^b have the following meanings: each R^1 is independently selected from H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, fluoro(C_1-C_8)alkyl, aryl, aryl(C_1-C_4)alkyl, $C(O)R^a$, CO_2R^a and $C(O)NR^aR^b$; each R^2 is independently selected from H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, fluoro(C_1-C_8)alkyl, $C(O)R^a$, CO_2R^a, $C(O)NR^aR^b$, aryl and aryl(C_1-C_4)alkyl; R^3 and R^4 are independently selected from H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, $C(O)R^a$, CO_2R^a, $C(O)NR^aR^b$ and (C_1-C_4)alkylene-OR^a; R^5 and R^6 are independently selected from H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, $C(O)R^a$ and CO_2R^a; R^7 is selected from H, (C_1-C_8)alkyl, halo(C_1-C_4)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, $C(O)R^a$, OR^a and NR^aR^b; and each R^a and R^b is independently selected from H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, fluoro(C_1-C_8)alkyl, aryl and aryl(C_1-C_4)alkyl.

[0013] The dotted line indicates an optional bond. In other optional embodiments, R^3 and R^4 may be combined to form a 3-, 4-, 5- or 6-membered spiro ring; R^2, R^3 or R^4 may be combined with W^1 to form a 5-, 6- or 7-membered fused ring having from 0 to 3 heteroatoms selected from the group consisting of N, O and S; R^5 and R^6 may be combined with the nitrogen atom to which each is attached to form a 5-, 6- or 7-membered ring; when X is $C(R^1)$, R^5 or R^6 may be combined with R^1 to form a 5-, 6- or 7-membered fused ring containing the nitrogen atom to which R^5 or R^6 is attached; when X is $C(R^1)$, R^7 may be combined with R^1 to form a 5-, 6- or 7-membered fused ring; R^2 or R^1, when provided as a part of Y, can be combined with R^5 to form a 5- or 6-membered ring with the nitrogen to which R^5 is attached, optionally bearing an oxo moiety; and when m is 1 and L^2 is a bond, a substituent on W^2 may be combined with a substituent on W^1 to form a 5-, 6- or 7-membered ring fused to W^1 and spiro or fused to W^2, wherein the ring is saturated or unsaturated and has 0, 1 or 2 heteroatoms selected from N, O and S as ring members.

[0014] Within the above compounds of formula I, the compound is other than



wherein R^8 is H, NO_2, Cl, methoxy, methyl or phenyl.

[0015] Unless otherwise indicated, the compounds provided in the above formula are meant to include all pharmaceutically acceptable salts, prodrugs or stereoisomers thereof.

[0016] The present invention also provides pharmaceutical compositions comprising a compound of the invention and a pharmaceutically acceptable carrier or excipient.

[0017] The present invention also provides methods for treating or preventing a condition or disorder selected from the group consisting of obesity, diabetes, anorexia nervosa, bulimia, cachexia, syndrome X, metabolic syndrome, insulin resistance, hyperglycemia, hyperuricemia, hyperinsulinemia, hypercholesterolemia, hyperlipidemia, dyslipidemia, mixed dyslipidemia, hypertriglyceridemia, nonalcoholic fatty liver disease, atherosclerosis, arteriosclerosis, acute heart failure, congestive heart failure, coronary artery disease, cardiomyopathy, myocardial infarction, angina pectoris, hypertension, hypotension, stroke, ischemia, ischemic reperfusion injury, aneurysm, restenosis, vascular stenosis, solid tumors, skin cancer, melanoma, lymphoma, breast cancer, lung cancer, colorectal cancer, stomach cancer, esophageal cancer, pancreatic cancer, prostate cancer, kidney cancer, liver cancer, bladder cancer, cervical cancer, uterine cancer, testicular cancer and ovarian cancer, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of the invention. For this method and the methods provided below, the compound of the invention will, in some embodiments, be administered in combination with a second therapeutic agent.

[0018] The present invention also provides methods for treating or preventing conditions and disorders associated with DGAT, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of the invention.

[0019] The present invention further provides methods for treating or preventing conditions and disorders mediated by DGAT, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of the invention.

[0020] The present invention further provides methods for modulating DGAT comprising contacting a cell with a compound of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] NOT APPLICABLE

DETAILED DESCRIPTION OF THE INVENTION

Abbreviations and Definitions

[0022] The terms "treat", "treating" and "treatment" refer to a method of alleviating or abrogating a disease and/or its attendant symptoms.

[0023] The terms "prevent", "preventing" and "prevention" refer to a method of preventing the onset of a disease and/or its attendant symptoms or barring a subject from acquiring a disease. As used herein, "prevent", "preventing" and "prevention" also include delaying the onset of a disease and/or its attendant symptoms and reducing a subject's risk of acquiring a disease.

[0024] The term "therapeutically effective amount" refers to that amount of the compound being administered sufficient to prevent development of or alleviate to some extent one or more of the symptoms of the condition or disorder being treated.

[0025] As used herein, "diabetes" refers to type I diabetes mellitus (juvenile onset diabetes, insulin dependent-diabetes mellitus or IDDM) or type II diabetes mellitus (non-insulin-dependent diabetes mellitus or NIDDM), preferably, type II diabetes.

[0026] As used herein, "syndrome X" refers to a collection of abnormalities including hyperinsulinemia, obesity, elevated levels of triglycerides, uric acid, fibrinogen, small dense LDL particles and plasminogen activator inhibitor 1 (PAI-1), and decreased levels of HDL cholesterol. Syndrome X is further meant to include metabolic syndrome.

[0027] As used herein, the term "obesity" refers to the excessive accumulation of body fat. Obesity may have genetic, environmental (*e.g.*, expending less energy than is consumed) and regulatory determinants. Obesity includes exogenous, hyperinsulinar, hyperplasmic, hypothyroid, hypothalamic, symptomatic, infantile, upper body, alimentary, hypogonadal, simple and central obesity, hypophyseal adiposity and hyperphagia. Metabolic disorders, such as hyperlidemia and diabetes, and cardiovascular disorders, such as hypertension and coronary artery disease, are commonly associated with obesity.

[0028] The term "modulate" refers to the ability of a compound to increase or decrease the function, or activity, of DGAT. "Modulation", as used herein in its various forms, is intended to encompass antagonism, agonism, partial antagonism and/or partial agonism of the activity associated with DGAT. DGAT inhibitors are compounds that, *e.g.*, bind to, partially or totally block stimulation, decrease, prevent, delay activation, inactivate, desensitize, or down

regulate signal transduction. DGAT activators are compounds that, *e.g.*, bind to, stimulate, increase, open, activate, facilitate, enhance activation, sensitize or up regulate signal transduction.

[0029] The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0030] The "subject" is defined herein to include animals such as mammals, including, but not limited to, primates (*e.g.*, humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In preferred embodiments, the subject is a human.

[0031] The term "DGAT" refers to the acyl CoA:diacylglycerol acyltransferase or a variant thereof, unless otherwise stated. DGAT variants include proteins substantially homologous to native DGAT, *i.e.*, proteins having one or more naturally or non-naturally occurring amino acid deletions, insertions or substitutions (*e.g.*, DGAT derivatives, homologs and fragments). The amino acid sequence of a DGAT variant preferably is at least about 80% identical to a native DGAT, more preferably at least about 90% identical, and most preferably at least about 95% identical.

[0032] As used herein, the term "DGAT-associated condition or disorder" refers to a condition or disorder associated with inappropriate, *e.g.*, less than or greater than normal, DGAT activity and at least partially responsive to or affected by DGAT modulation (*e.g.*, a DGAT inhibitor or antagonist results in some improvement in patient well-being in at least some patients). Inappropriate DGAT functional activity might arise as the result of DGAT expression in cells which normally do not express DGAT decreased DGAT expression or increased DGAT expression. A DGAT-associated condition or disorder may include a DGAT-mediated condition or disorder.

[0033] As used herein, the term "DGAT-mediated condition or disorder" and the like refers to a condition or disorder characterized by inappropriate, *e.g.*, less than or greater than normal, DGAT activity. A DGAT-mediated condition or disorder may be completely or partially mediated by inappropriate DGAT activity. However, a DGAT-mediated condition or disorder is one in which modulation of DGAT results in some effect on the underlying

condition or disease (*e.g.*, a DGAT inhibitor or antagonist results in some improvement in patient well-being in at least some patients).

[0034] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which is fully saturated, having the number of carbon atoms designated (*i.e.* C_1-C_8 means one to eight carbons). Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl and the like.

[0035] The term "alkenyl", by itself or as part of another substituent, means a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be mono- or polyunsaturated, having the number of carbon atoms designated (*i.e.* C_2-C_8 means two to eight carbons) and one or more double bonds. Examples of alkenyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl) and higher homologs and isomers thereof.

[0036] The term "alkynyl", by itself or as part of another substituent, means a straight or branched chain hydrocarbon radical, or combination thereof, which may be mono- or polyunsaturated, having the number of carbon atoms designated (*i.e.* C_2-C_8 means two to eight carbons) and one or more triple bonds. Examples of alkynyl groups include ethynyl, 1- and 3-propynyl, 3-butynyl and higher homologs and isomers thereof.

[0037] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from alkyl, as exemplified by $-CH_2CH_2CH_2CH_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. Similarly, "alkenylene" and "alkynylene" refer to unsaturated versions of alkylene, having at least one double bond or a triple bond, respectively. For example, "alkenylene" is meant to include $-CH_2CH{=}CHCH_2-$, while "alkynylene" is meant to include $-CH_2C{\equiv}CCH_2-$.

[0038] The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule *via* an oxygen atom, an amino group, or a sulfur atom, respectively.

[0039] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, Si and S, wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. The heteroatom Si may be placed at any position of the heteroalkyl group, including the position at which the alkyl group is attached to the remainder of the molecule. Examples include $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2,-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, and $-CH=CH-N(CH_3)-CH_3$. Up to two heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$.

[0040] Similarly, the term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified by $-CH_2-CH_2-S-CH_2CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (*e.g.*, alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied.

[0041] The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Accordingly, a cycloalkyl group has the number of carbon atoms designated (*i.e.*, C_3-C_8 means three to eight carbons) and may also have one or two double bonds. A heterocycloalkyl group consists of the number of carbon atoms designated and from one to three heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include 1 -(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

[0042] The terms "halo" and "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include alkyl substituted with halogen atoms, which can be the same or different, in a number ranging from one to (2m' + 1), where m' is the total number of carbon atoms in the alkyl group. For example, the term "halo(C_1-C_4)alkyl" is mean to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like. Thus, the term "haloalkyl" includes monohaloalkyl (alkyl substituted with one halogen atom) and polyhaloalkyl (alkyl substituted with halogen atoms in a number ranging from two to (2m' + 1) halogen atoms, where m' is the total number of carbon atoms in the alkyl group). The term "perhaloalkyl" means, unless otherwise stated, alkyl substituted with (2m' + 1) halogen atoms, where m' is the total number of carbon atoms in the alkyl group. For example the term "perhalo(C_1-C_4)alkyl" is meant to include trifluoromethyl, pentachloroethyl, 1,1,1-trifluoro-2-bromo-2-chloroethyl and the like.

[0043] The term "aryl" means, unless otherwise stated, a polyunsaturated, typically aromatic, hydrocarbon substituent which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. Non-limiting examples of aryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl and 1,2,3,4-tetrahydronaphthalene.

[0044] The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized and the nitrogen heteroatom are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of heteroaryl groups include 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl and 6-quinolyl.

[0045] For brevity, the term "aryl" when used in combination with other terms (*e.g.*, aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (*e.g.*, benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (*e.g.*, a methylene group) has been replaced by, for

example, an oxygen atom (*e.g.*, phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like).

[0046] Each of the above terms (*e.g.*, "alkyl," "heteroalkyl," "aryl" and "heteroaryl") is meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0047] Substituents for the alkyl and heteroalkyl radicals (as well as those groups referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl and heterocycloalkenyl) can be a variety of groups selected from: -OR', =O, =NR', =N-OR', -NR'R", -SR', halogen, -SiR'R"R"', -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', $-NR'-SO_2NR"R"'$, $-NR"CO_2R'$, $-NH-C(NH_2)=NH$, $-NR'C(NH_2)=NH$, $-NH-C(NH_2)=NR'$, -S(O)R', $-SO_2R'$, $-SO_2NR'R"$, $-NR"SO_2R'$, -CN and $-NO_2$, in a number ranging from zero to three, with those groups having zero, one or two substituents being particularly preferred. R', R" and R"' each independently refer to hydrogen, unsubstituted (C_1-C_8)alkyl and heteroalkyl, unsubstituted aryl, aryl substituted with one to three halogens, unsubstituted alkyl, alkoxy or thioalkoxy groups, or aryl-(C_1-C_4)alkyl groups. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6- or 7-membered ring. For example, -NR'R" is meant to include 1-pyrrolidinyl and 4-morpholinyl. Additionally, the above substituents can be attached to the alkyl group (or alkylene, cycloalkyl and the like) via a spacer of from one to four carbon atoms, generally present as methylene or branched unsubstituted alkylene (e.g. $-CH_2CH_2-$ and $-CH(CH_3)CH_2-$), alkenylene or alkynylene group. Typically, an alkyl or heteroalkyl group will have from zero to three substituents, with those groups having two or fewer substituents being preferred in the present invention. More preferably, an alkyl or heteroalkyl radical will be unsubstituted or monosubstituted. Most preferably, an alkyl or heteroalkyl radical will be unsubstituted. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups such as trihaloalkyl (*e.g.*, $-CF_3$ and $-CH_2CF_3$).

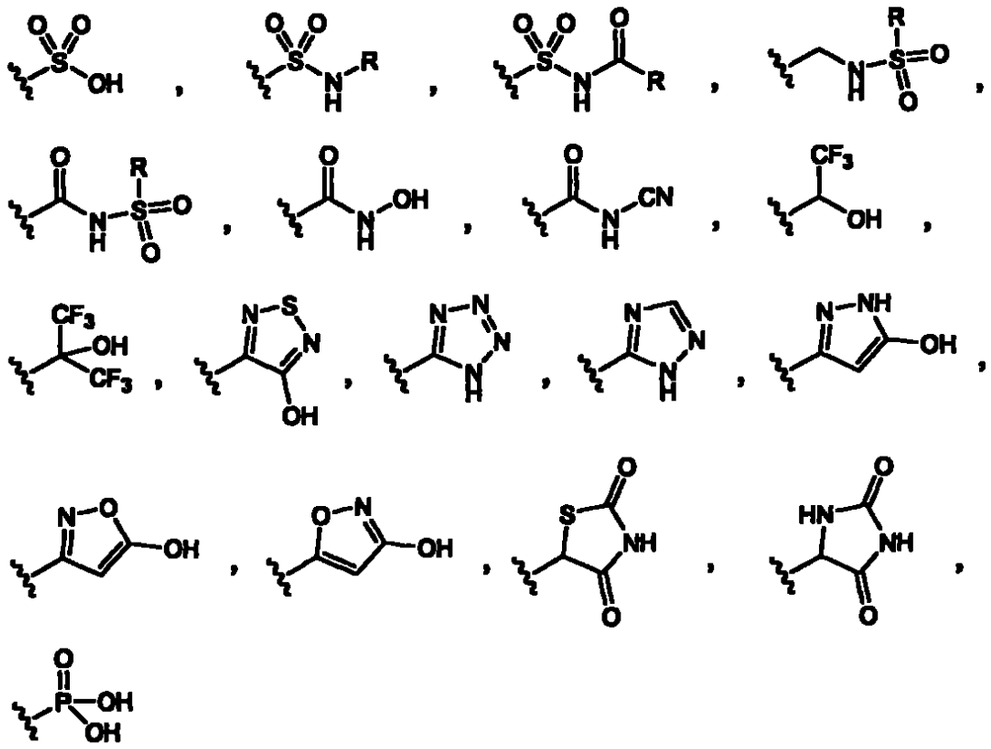
[0048] Preferred substituents for the alkyl and heteroalkyl radicals are selected from: -OR', =O, -NR'R", -SR', halogen, -SiR'R"R"', -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', $-NR"CO_2R'$, $-NR'-SO_2NR"R"'$, -S(O)R', $-SO_2R'$, $-SO_2NR'R"$, $-NR"SO_2R'$, -CN and $-NO_2$, where R' and R" are as defined above. Further preferred substituents are selected from: -OR', =O, -NR'R", halogen, -OC(O)R', $-CO_2R'$, -CONR'R",

-OC(O)NR'R", -NR"C(O)R', -NR"CO_2R', -NR'-SO_2NR"R"', -SO_2R', -SO_2NR'R", -NR"SO_2R, -CN and -NO_2. Additionally, each of the preferred and further preferred substituents can be attached to the alkyl group (or alkylene, cycloalkyl and the like) via a spacer of from one to four carbon atoms, generally present as methylene or branched unsubstituted alkylene groups.

[0049] Similarly, substituents for the aryl and heteroaryl groups are varied and selected from: halogen, -OR', -OC(O)R', -NR'R", -SR', -R', -CN, -NO_2, -CO_2R', -CONR'R", -C(O)R', -OC(O)NR'R", -NR"C(O)R', -NR"CO_2R', -NR'-C(O)NR"R"', -NR'-SO_2NR"R"', -NH-C(NH_2)=NH, -NR'C(NH_2)=NH, -NH-C(NH_2)=NR', -S(O)R', -SO_2R', -SO_2NR'R", -NR"SO_2R', -N_3, -CH(Ph)$_2$, perfluoro(C_1-C_4)alkoxy and perfluoro(C_1-C_4)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R" and R"' are independently selected from hydrogen, (C_1-C_8)alkyl and heteroalkyl, unsubstituted aryl and heteroaryl, (unsubstituted aryl)-(C_1-C_4)alkyl and (unsubstituted aryl)oxy-(C_1-C_4)alkyl. When the aryl group is 1,2,3,4-tetrahydronaphthalene, it may be substituted with a substituted or unsubstituted (C_3-C_7)spirocycloalkyl group. The (C_3-C_7)spirocycloalkyl group may be substituted in the same manner as derined herein for "cycloalkyl". Typically, an aryl or heteroaryl group will have from zero to three substituents, with those groups having two or fewer substituents being preferred in the present invention. In one embodiment of the invention, an aryl or heteroaryl group will be unsubstituted or monosubstituted. In another embodiment, an aryl or heteroaryl group will be unsubstituted. When substituted, the above substituents can be attached to the aryl or heteroaryl group via a spacer of from one to four carbon atoms, generally present as methylene or branched unsubstituted alkylene groups (e.g. -CH_2CH_2- and -$CH(CH_3)CH_2$-).

[0050] Preferred substituents for aryl and heteroaryl groups are selected from: halogen, -OR', -OC(O)R', -NR'R", -SR', -R', -CN, -NO_2, -CO_2R', -CONR'R", -C(O)R', -OC(O)NR'R", -NR"C(O)R', -S(O)R', -SO_2R', -SO_2NR'R", -NR"SO_2R', -N_3, -CH(Ph)$_2$, perfluoro(C_1-C_4)alkoxy and perfluoro(C_1-C_4)alkyl, where R' and R" are as defined above. Further preferred substituents are selected from: halogen, -OR', -OC(O)R', -NR'R", -R', -CN, -NO_2, -CO_2R', -CONR'R", -NR"C(O)R', -SO_2R', -SO_2NR'R", -NR"SO_2R', perfluoro(C_1-C_4)alkoxy and perfluoro(C_1-C_4)alkyl. As above, these substituents are optionally attached to the aryl or heteroaryl moiety via a spacer of from one to four methylene groups.

[0051] It is to be understood that the substituent $-CO_2H$, as used herein, includes bioisosteric replacements therefor, such as:



and the like. See, *e.g.*, *The Practice of Medicinal Chemistry*; Wermuth, C.G., Ed.; Academic Press: New York, 1996; p. 203.

[0052] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-$(CH_2)_q$-U-, wherein T and U are independently -NH-, -O-, -CH_2- or a single bond, and q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently -CH_2-, -O-, -NH-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$NR'- or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -$(CH_2)_s$-X-$(CH_2)_t$-, where s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituent R' in -NR'- and -$S(O)_2$NR'- is selected from hydrogen or unsubstituted (C_1-C_6)alkyl.

[0053] As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

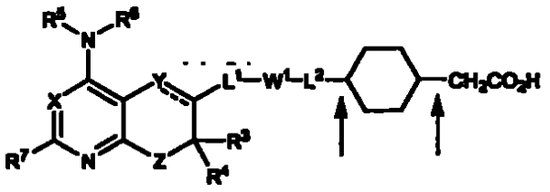
[0054] The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the free acid form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the free base form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., et al, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, 1977, *66*, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0055] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

[0056] In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example,

prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0057] It is to be understood that when a compound of the invention contains one or more asymmetric carbon atoms (optical centers) or double bonds, the present invention includes individual stereoisomers and geometric isomers as well as mixtures thereof. For example, when m is 1 and W^2 is substituted cyclo(C_3-C_8)alkyl (*e.g.*, A.4 below), the 1,4-*cis* and *trans* isomers and racemates thereof are intended to be within the scope of the invention.



A.4

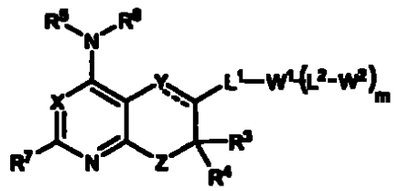
[0058] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0059] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

Embodiments of the Invention

Compounds

In one aspect, the present invention provides compounds of formula (I):



13

I

or a pharmaceutically acceptable salt, prodrug or stereoisomer thereof. In this formula, the letter X represents $C(R^1)$ or N; the letter Y represents $C(R^1)$, $C(R^2)(R^2)$, N or $N(R^2)$; and the letter Z represents O or S.

[0060] Turning next to the substituents on the bicyclic heteroaromatic nucleus, the symbol L^1 represents a bond, $(C_1\text{-}C_4)$alkylene, $(C_2\text{-}C_4)$alkenylene, O or $N(R^a)C(O)$; and W^1 represents a substituted or unsubstituted member selected from cyclo$(C_3\text{-}C_8)$alkyl, heterocyclo$(C_3\text{-}C_8)$alkyl, aryl and heteroaryl. The subscript m is 0 or 1, indicating the presence (m is 1) or absence (m is 0) of the additional moiety, $L^2\text{-}W^2$. For those embodiments in which m is 1, the symbol L^2 represents a bond, O, $(C_1\text{-}C_4)$alkylene, $(C_2\text{-}C_4)$alkenylene, $(C_1\text{-}C_4)$heteroalkylene or $N(R^a)C(O)$; and the symbol W^2 represents a substituted or unsubstituted member selected from cyclo$(C_3\text{-}C_8)$alkyl, heterocyclo$(C_3\text{-}C_8)$alkyl, aryl and heteroaryl. When m is 1 and L^2 is a bond, a substituent on W^2 may be combined with a substituent on W^1 to form a 5-, 6- or 7-membered ring fused to W^1 and spiro or fused to W^2, wherein the ring is saturated or unsaturated and has 0, 1 or 2 heteroatoms selected from N, O and S as ring members. Substituents for each of W^1 and W^2 can be selected from the substituents provided in the definitions above as well as the recited substituents for various specific embodiments below.

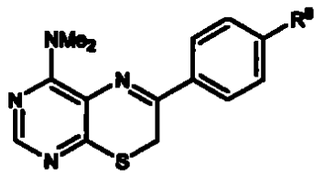
[0061] The remaining substituents, R^1 through R^7 and R^a and R^b have the following meanings: each R^1 is independently selected from H, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, fluoro$(C_1\text{-}C_8)$alkyl, aryl, aryl$(C_1\text{-}C_4)$alkyl, $C(O)R^a$, CO_2R^a and $C(O)NR^aR^b$; each R^2 is independently selected from H, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, fluoro$(C_1\text{-}C_8)$alkyl, $C(O)R^a$, CO_2R^a, $C(O)NR^aR^b$, aryl and aryl$(C_1\text{-}C_4)$alkyl; R^3 and R^4 are independently selected from H, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $C(O)R^a$, CO_2R^a, $C(O)NR^aR^b$ and $(C_1\text{-}C_4)$alkylene-OR^a; R^5 and R^6 are independently selected from H, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $C(O)R^a$ and CO_2R^a; R^7 is selected from H, $(C_1\text{-}C_8)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, $C(O)R^a$, OR^a and NR^aR^b; and each R^a and R^b is independently selected from H, $(C_1\text{-}C_8)$alkyl, $(C_2\text{-}C_8)$alkenyl, $(C_2\text{-}C_8)$alkynyl, fluoro$(C_1\text{-}C_8)$alkyl, aryl and aryl$(C_1\text{-}C_4)$alkyl.

[0062] The dotted line indicates an optional bond. In other optional embodiments, R^3 and R^4 may be combined to form a 3-, 4-, 5- or 6-membered spiro ring; R^2, R^3 or R^4 may be combined with W^1 to form a 5-, 6- or 7-membered fused ring having from 0 to 3 heteroatoms

selected from the group consisting of N, O and S; R^5 and R^6 may be combined with the nitrogen atom to which each is attached to form a 5-, 6- or 7-membered ring; R^2 or R^1, when provided as a part of Y, can be combined with R^5 to form a 5- or 6-membered ring with the nitrogen to which R^5 is attached, optionally bearing an oxo moiety; when X is $C(R^1)$, R^5 or R^6 may be combined with R^1 to form a 5-, 6- or 7-membered fused ring containing the nitrogen atom to which R^5 or R^6 is attached; and when X is $C(R^1)$, R^7 may be combined with R^1 to form a 5-, 6- or 7-membered fused ring.

[0063] In preferred embodiments, R^1 and R^2 are each independently H or $(C_1$-$C_8)$alkyl; R^3 and R^4 are each independently H or $(C_1$-$C_4)$alkyl; R^5 and R^6 are each H, $(C_1$-$C_4)$alkyl or are combined with the nitrogen to which each is attached to form a 5- or 6-membered ring (*e.g.* a pyrollidine or piperidine ring); and R^7 is H, $(C_1$-$C_8)$alkyl or halo$(C_1$-$C_4)$alkyl.

[0064] Within the above compounds of formula (I), the compound is other than



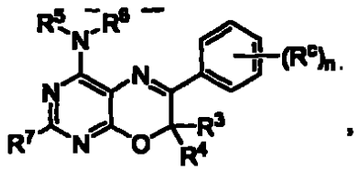
wherein R^8 is H, NO_2, Cl, methoxy, methyl or phenyl.

[0065] Within formula (I) above, a number of groups of embodiments are preferred.

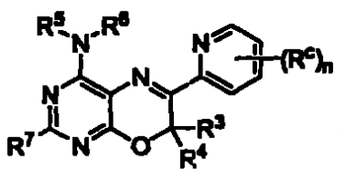
[0066] In one group of preferred embodiments, X is N. Still more preferably, X is N and Z is O. Within this group of embodiments, L^1 is preferably a bond and W^1 is a substituted or unsubstituted member selected from benzene, pyridine, thiophene, oxazole, thiazole, benzoxazole, benzthiazole, benzofuran, benzothiophene, $(C_4$-$C_7)$cycloalkane, $(C_5$-$C_7)$cycloalkene, 1,2,3,4-tetrahydronaphthalene and indane. Still more preferably, W^1 is a substituted or unsubstituted member selected from benzene, pyridine, thiophene, $(C_4$-$C_7)$cycloalkane, 1,2,3,4-tetrahydronaphthalene and indane. For those embodiments in which W^1 is a substituted benzene, the substituents (R^c below), other than L^2-W^2, are preferably selected from halogen (including F, Cl, Br and I), R^{c1}, OR^{c1}, $N(R^{c1})_2$, SR^{c1}, NO_2, CN, $(C_1$-$C_8)$haloalkyl and $(C_1$-$C_8)$haloalkoxy, wherein each R^{c1} group is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl or $(C_2$-$C_8)$alkynyl, and optionally, two R^{c1} groups attached to a common nitrogen atom are combined to form a five- or six membered ring. Additionally, the substituted benzene will preferably have from one to four substituents, more preferably one or two substitutents and most preferably one substituent. Substituents for each of W^1 and W^2

can be selected from the substituents provided in the definitions above as well as the recited substituents for various specific embodiments below.

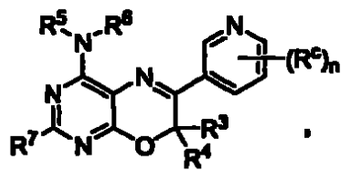
[0067] In one group of specific embodiments, the subscript m is 0 and L^1 is a bond. Still more preferably, W^1 is selected from a substituted or unsubstituted benzene, pyridine, thiophene, oxazole, thiazole, benzoxazole, benzthiazole, benzofuran, benzothiophene, (C_4-C_7)cycloalkane, (C_5-C_7)cycloalkene, 1,2,3,4-tetrahydronaphthalene and indane. Still more preferably, W^1 is a substituted or unsubstituted member selected from benzene, pyridine, thiophene, (C_4-C_7)cycloalkane, 1,2,3,4-tetrahydronaphthalene and indane. Even further preferred are those embodiments depicted as formulae Ia, Ib, Ic, Id, Ie, If and Ig below:



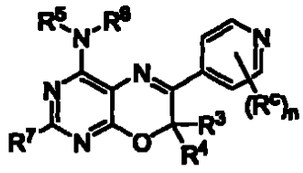
Ia



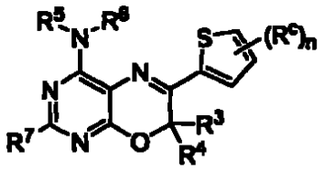
Ib



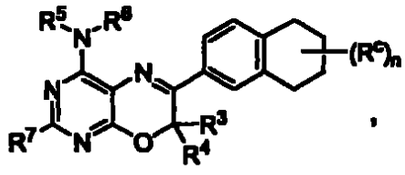
Ic



Id

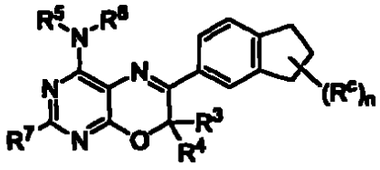


Ie



If

and

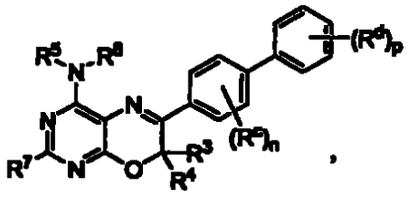


Ig

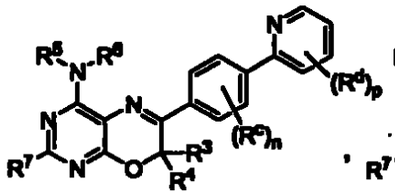
wherein the subscript n is an integer of from 0 to 4 and each R^c represents a substituent independently selected from halogen (including F, Cl, Br and I), R^{c1}, OR^{c1}, $N(R^{c1})_2$, SR^{c1}, NO_2, CN, (C_1-C_8)haloalkyl and (C_1-C_8)haloalkoxy, wherein each R^{c1} group is independently H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl or (C_2-C_8)alkynyl and when R^c is $N(R^{c1})_2$, the two R^{c1} groups may be combined to form a five- or six-membered ring. Optionally, for If and Ig, two R^{c1} groups may be combined to form a 3-, 4-, 5-, 6- or 7-membered optionally substituted spirocyclic ring. The remaining substitutents have the meanings provided above with respect to the general formula I.

[0068] In a related group of specific embodiments, X is N, Z is O, L^1 is preferably a bond, W^1 is a substituted or unsubstituted member selected from benzene, pyridine, thiophene, oxazole, thiazole, benzoxazole, benzthiazole, benzofuran, benzothiophene, (C_4-C_7)cycloalkane, (C_5-C_7)cycloalkene, 1,2,3,4-tetrahydronaphthalene and indane, and m is 1. In this group of embodiments, L^2 is preferably a bond, O, or a (C_1-C_4)heteroalkylene (*e.g.*, -OCH_2-, -OCH_2CH_2-, -$NHCH_2$-) and W^2 is a substituted or unsubstituted member selected from benzene, pyridine and (C_4-C_7)cycloalkane.

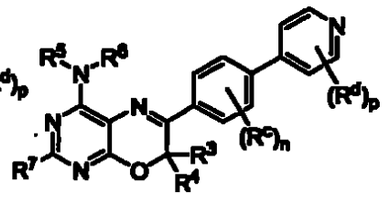
[0069] In one group of particularly preferred embodiments, the compound is selected from the group:



Ih

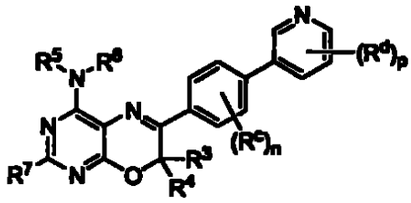


Ii



Ij

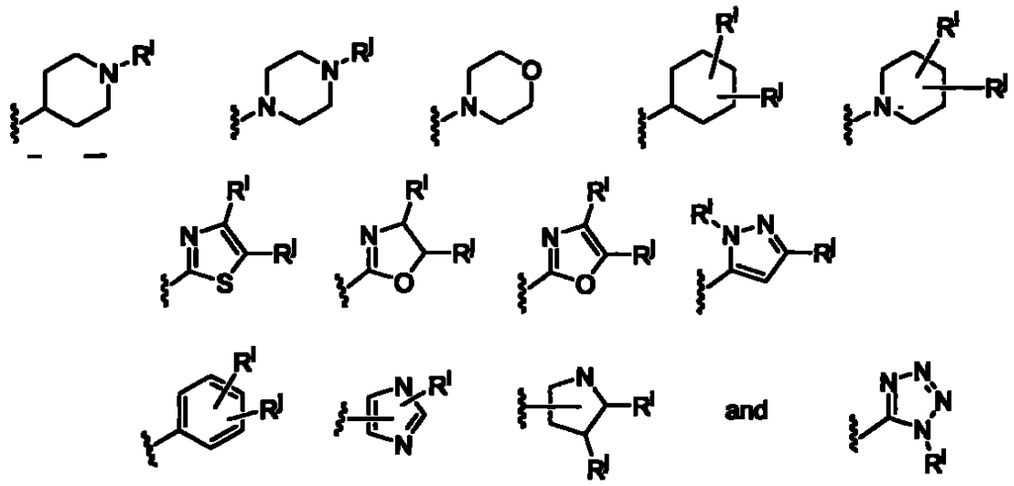
and



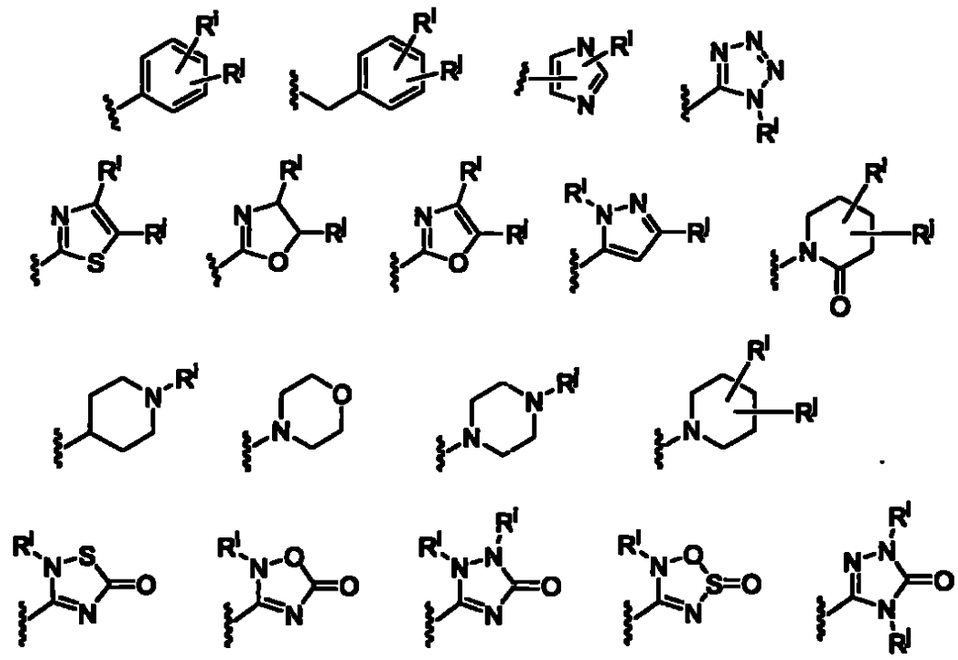
Ik

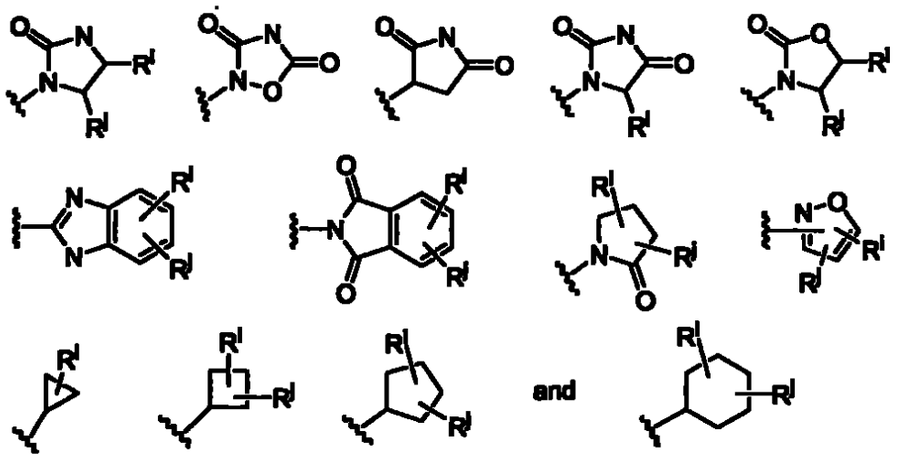
wherein the subscript n is an integer of from 0 to 4 and each R^c represents a substituent independently selected from halogen (including F, Cl, Br and I), R^{c1}, OR^{c1}, $N(R^{c1})_2$, SR^{c1}, NO_2, CN, (C_1-C_8)haloalkyl and (C_1-C_8)haloalkoxy, wherein each R^{c1} group is independently H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl or (C_2-C_8)alkynyl, and optionally, two R^{c1} groups attached to a common nitrogen atom are combined to form a five- or six membered ring. Additionally, the subscript p is an integer of from 0 to 4, more preferably 0, 1 or 2, and each R^d is a substituent independently selected from halogen (including F, Cl, Br and I), R^{d1}, OR^{d1}, $N(R^{d1})_2$, -$(CH_2)_t$-$S(O)_uR^e$, NO_2, CN, (C_1-C_8)haloalkyl, (C_1-C_8)haloalkoxy, aryl(C_1-C_4)alkyl, heteroaryl(C_1-C_4)alkyl, -$CH(R^f)$-CO_2R^e, -$C(R^f)_2$-CO_2R^e, -$C(O)CO_2R^e$, -$(CH_2)_t$-CO_2R^e, -$(CH_2)_t$-$C(O)R^e$, -$(CH_2)_t$-$C(O)NR^eR^f$, -$(CH_2)_t$-$NHSO_2R^e$, -$(CH_2)_t$-$SO_2NR^eR^f$, -$(CH_2)_t$-NR^eR^f, -$(CH_2)_t$-OR^e, -$(CH_2)_t$-$NHSO_2NHCO_2R^e$, -$(CH_2)_t$-$NHSO_2NR^eR^f$, -$(CH_2)_t$-$CONHSO_2R^e$, -$(CH_2)_t$-W^3, -$(CH_2)_t$-$NHCO_2R^e$, -$(CH_2)_t$-NR^fCOR^e, -$(CH_2)_t$-$NHCONR^eR^f$ and -$(CH_2)_t$-$NHCO$-$(CH_2)_t$-$OCOR^e$, wherein the subscript t in each instance is an integer of from

0 to 8, the subscript u is an integer of from 0 to 2, R^{d1} is selected from H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl and (C_3-C_8)cycloalkyl, wherein the aliphatic portion is optionally substituted with OH, CO_2H, NH_2, $CONH_2$, phenyl, halogen, halo(C_1-C_4)alkyl and CO_2R^g, and optionally two R^{d1} groups attached to a common nitrogen are combined to form a five or six-membered ring; and wherein each R^e and R^f is independently H or (C_1-C_8)alkyl or when attached to a common nitrogen atom are combined to form a 5- or 6-membered ring, or are optionally selected from



and wherein any alkyl portion of R^e and R^f is optionally substituted with a member selected from OH, COOH, NH_2, $CONH_2$, phenyl, dialkylamino and $COOR^g$ wherein R^g is a (C_1-C_4)alkyl; and W^3 is selected from



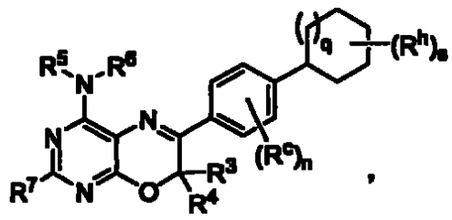


wherein each R^I and each R^J is independently selected from H, OH, COOH, halogen, halo(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_4)alkyl and $COO(C_1$-$C_4)$alkyl, wherein the aliphatic portions are unsubstituted or optionally substituted with halogen.

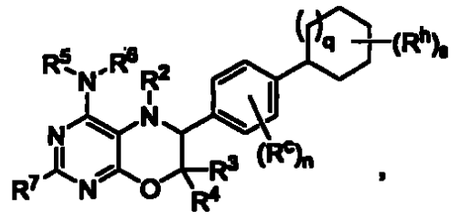
[0070] In some embodiments, the R^d substituents are selected from halogen (including F, Cl, Br and I), R^{d1}, OR^{d1}, $N(R^{d1})_2$, SR^{d1}, NO_2, CN, (C_1-C_8)haloalkyl, (C_1-C_8)haloalkoxy, aryl(C_1-C_4)alkyl, heteroaryl(C_1-C_4)alkyl, (C_1-C_8)alkylene-CO_2R^e, $C(O)R^e$, CO_2R^e, $-CH_2$-CO_2R^e, $-CH(R^f)$-CO_2R^e, $-C(R^f)_2$-CO_2R^e, $-CH_2CH_2CO_2R^e$, $-C(O)NR^eR^f$, $-CH_2C(O)NR^eR^f$, $-CH_2CH_2CONR^eR^f$, $-NHSO_2R^e$, $-CH_2NHSO_2R^e$, $-CH_2CH_2NHSO_2R^e$, $-CH_2SO_2NR^eR^f$, $-CH_2CH_2SO_2NR^eR^f$, $-CH_2OH$, $-CH_2NR^eR^f$, CH_2CH_2OH, $-CH_2C(CH_3)_2OH$, $-CH_2$-W^3, $-CH_2CH_2$-W^3 and $-C(O)CO_2R^e$, wherein each R^{d1}, R^e, R^f and W^3 have the meanings provided above, with respect to formulae Ih, Ii, Ij and Ik, and the remaining substitutents have the meanings provided above with respect to the general formula I.

[0071] In still other preferred embodiments, the compound has a formula selected from:

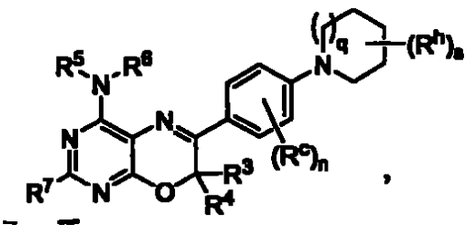
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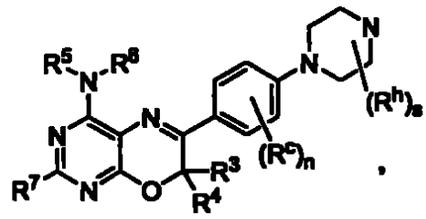
Il



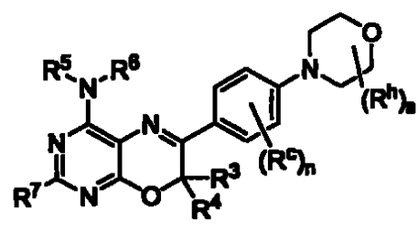
Im



In

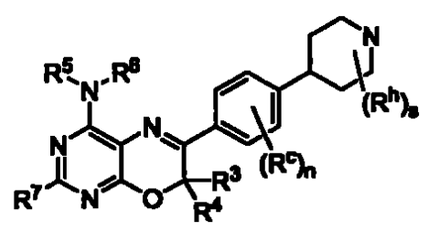


Io



Ip

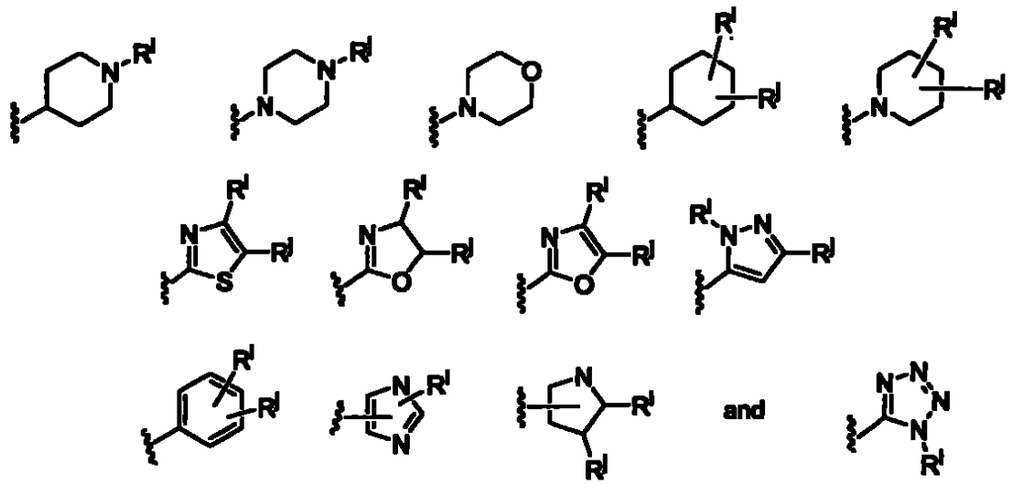
and



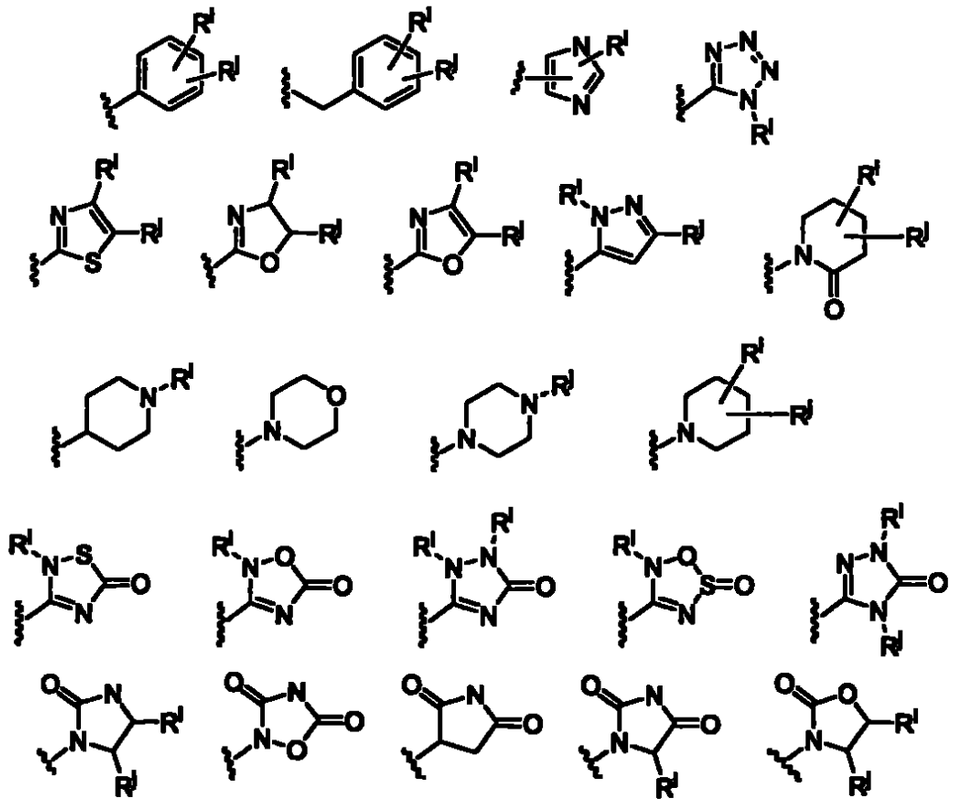
Iq

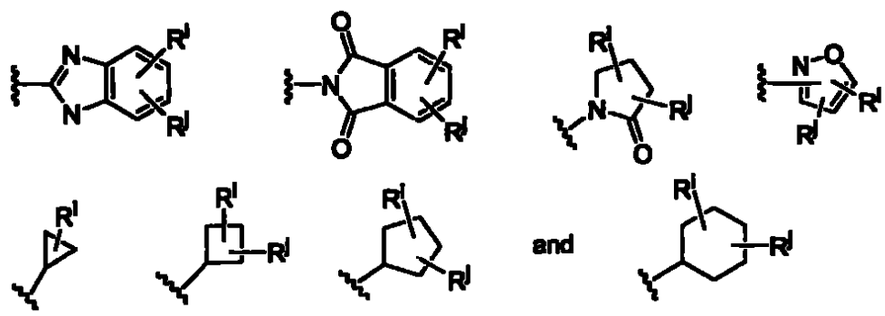
wherein each of R^2, R^3, R^4, R^5, R^6, R^7 and R^c, as well as the subscript n have the meanings provided above with respect to formulae Ia-Ik. The subscript q is an integer of from 0 to 3, more preferably, 0 or 1. The subcript s is an integer of from 0 to 4, more preferably 0, 1 or 2, and each R^h is a substituent independently selected from oxo, halogen (including F, Cl, Br and I), R^{hl}, OR^{hl}, $N(R^{hl})_2$, $-(CH_2)_t-S(O)_uR^e$, NO_2, CN, (C_1-C_8)haloalkyl, (C_1-C_8)haloalkoxy, aryl(C_1-C_4)alkyl, heteroaryl(C_1-C_4)alkyl, $-CH(R^f)-CO_2R^e$, $-C(R^f)_2-CO_2R^e$, $-C(O)CO_2R^e$, $=CH-CONR^eR^f$, $=CH-CO_2R^e$, $-(CH_2)_t-CO_2R^e$, $-(CH_2)_t-C(O)R^e$, $-(CH_2)_t-C(O)NR^eR^f$, $-(CH_2)_t-NHSO_2R^e$, $-(CH_2)_t-SO_2NR^eR^f$, $-(CH_2)_t-NR^eR^f$, $-(CH_2)_t-OR^e$, $-(CH_2)_t-NHSO_2NHCO_2R^e$, $-(CH_2)_t-NHSO_2NR^eR^f$, $-(CH_2)_t-CONHSO_2R^e$, $-(CH_2)_t-W^3$, $-(CH_2)_t-NHCO_2R^e$, $-(CH_2)_t-NR^fCOR^e$, $-(CH_2)_t-NHCONR^eR^f$ and $-(CH_2)_t-NHCO-(CH_2)_t-OCOR^e$, wherein the subscript t in each instance is an integer of from 0 to 8, the subscript u is an integer of from 0 to 2, R^{hl} is selected from H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl and (C_3-C_8)cycloalkyl, wherein the aliphatic portion is optionally substituted with OH, CO_2H, NH_2, $CONH_2$, phenyl, halogen, halo(C_1-C_4)alkyl and CO_2R^g, and optionally two R^{hl} groups attached to a common nitrogen are combined to form a five or six-membered ring, or a R^h and an R^{hl} group may be combined to form a 3-, 4-, 5- or 6-

membered spiro or fused ring having from zero to two heteroatoms selected from N, O and S; and wherein each R^e and R^f is independently H or (C_1-C_8)alkyl or when attached to a common nitrogen atom are combined to form a 5- or 6-membered ring, or are optionally selected from



and wherein any alkyl portion of R^e and R^f is optionally substituted with a member selected from OH, COOH, NH_2, $CONH_2$, phenyl, dialkylamino and $COOR^g$ wherein R^g is a (C_1-C_4)alkyl; and W^3 is selected from



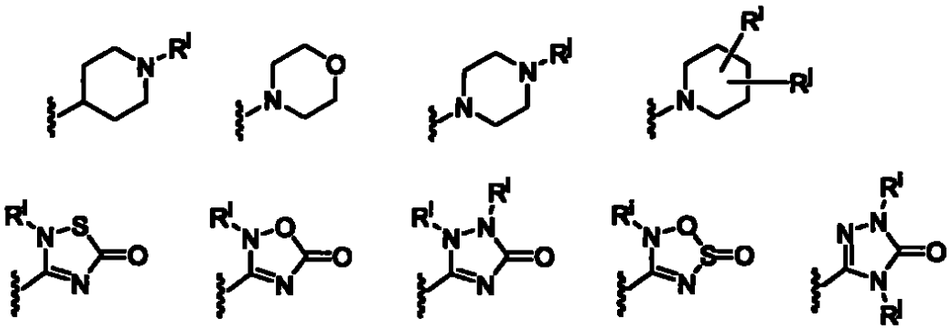


wherein each R^i and each R^j is independently selected from H, OH, COOH, halogen, halo(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkoxy(C_1-C_4)alkyl and COO(C_1-C_4)alkyl, wherein the aliphatic portions are unsubstituted or optionally substituted with halogen.

[0072] In some embodiments, the R^h substituents are selected from oxo, halogen (including F, Cl, Br and I), R^{hl}, OR^{hl}, $N(R^{hl})_2$, SR^{hl}, NO_2, CN, (C_1-C_8)haloalkyl, (C_1-C_8)haloalkoxy, aryl(C_1-C_4)alkyl, heteroaryl(C_1-C_4)alkyl, (C_1-C_8)alkylene-CO_2R^e, $C(O)R^e$, CO_2R^e, $=CH\text{-}CONR^eR^f$, $=CH\text{-}CO_2R^e$, $-CH_2\text{-}CO_2R^e$, $-CH(R^f)\text{-}CO_2R^e$, $-C(R^f)_2\text{-}CO_2R^e$, $-CH_2CH_2CO_2R^e$, $-C(O)NR^eR^f$, $-CH_2C(O)NR^eR^f$, $-CH_2CH_2CONR^eR^f$, $-NHSO_2R^e$, $-CH_2NHSO_2R^e$, $-CH_2CH_2NHSO_2R^e$, $-CH_2SO_2NR^eR^f$, $-CH_2CH_2SO_2NR^eR^f$, $-CH_2OH$, $-CH_2NR^eR^f$, CH_2CH_2OH, $-CH_2C(CH_3)_2OH$, $-CH_2\text{-}W^3$, $-CH_2CH_2\text{-}W^3$ and $-C(O)CO_2R^e$, wherein R^{hl}, R^e, R^f and W^3 have the meanings provided above, with respect to formulae II, Im, In, Io, Ip and Iq, and the remaining substitutents have the meanings provided above with respect to the general formula I.

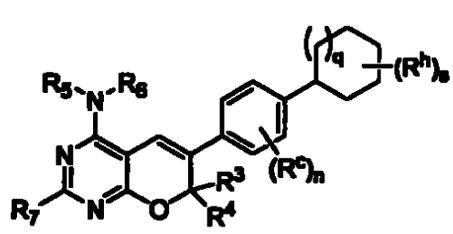
[0073] In some embodiments of each of formulae Ia through Iq, R^2 (when present) is H or a (C_1-C_8)alkyl; R^3 and R^4 are each independently H, (C_1-C_4)alkyl or are combined to form a 3-, 4-, 5- or 6-membered spirocyclic ring; R^5 and R^6 are each H, (C_1-C_4)alkyl or are combined with the nitrogen to which each is attached to form a 5- or 6-membered ring (*e.g.* a pyrollidine or piperidine ring); and R^7 is H, (C_1-C_8)alkyl or halo(C_1-C_4)alkyl. Still further preferred are those embodiments in which the subscript n is 0, q is 1 and s is 1. In a particularly preferred group of embodiments, the compound has the formula II, Im or In, and R^h represents a substituent having the formula $C(O)R^e$, CO_2R^e, $=CH\text{-}CO_2R^e$, $-CH_2\text{-}CO_2R^e$, $-CH_2NHCOR^e$, $-CH(R^f)\text{-}CO_2R^e$, $-C(R^f)_2\text{-}CO_2R^e$, $-CH_2CH_2CO_2R^e$, $-C(O)NR^eR^f$, $=CH\text{-}CONR^eR^f$, $-CH_2C(O)NR^eR^f$, $-CH_2CH_2C(O)NR^eR^f$, $-CH_2CH_2NHCO_2R^e$, $-CH_2NHCO_2R^e$, $-NHSO_2R^e$, $-CH_2NHSO_2R^e$, $-CH_2CH_2NHSO_2R^e$, $-CH_2SO_2NR^eR^f$, $-CH_2CH_2SO_2NR^eR^f$, $-CH_2OH$, $-CH_2NR^eR^f$, $-CH_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2\text{-}W^3$, $-CH_2CH_2\text{-}W^3$, $-C(O)CO_2R^e$ or $-CH_2\text{-}C(CF_3)_2\text{-}OH$. In an additional group of preferred embodiments, the compounds have

the formula II in which R^3 and R^4 are independently H or unsubstituted (C_1-C_4)alkyl; R^5 and R^6 are independently H or unsubstituted (C_1-C_4)alkyl; R^7 is selected from H, unsubstituted (C_1-C_4)alkyl or halo(C_1-C_4)alkyl; the subscript n is 0, 1 or 2 and R^c is selected from fluoro, chloro, bromo, cyano, methyl, trifluoromethyl and nitro; R^h is selected from CO_2R^e, $=CH-CO_2R^e$, $-CH_2-CO_2R^e$, $-CH_2NHCOR^e$, $-CH(R^f)-CO_2R^e$, $-C(R^f)_2-CO_2R^e$, $-CH_2CH_2CO_2R^e$, $-C(O)NR^eR^f$, $=CH-CONR^eR^f$, $-CH_2C(O)NR^eR^f$, $-CH_2CH_2C(O)NR^eR^f$, $-CH_2CH_2NHCO_2R^e$, $-CH_2NHCO_2R^e$, $-CH_2NR^eR^f$, $-CH_2-W^3$ and $-CH_2CH_2-W^3$; wherein each R^e and R^f is H or (C_1-C_4)alkyl optionally substituted with a member selected from OH, COOH, NH_2, $CONH_2$, phenyl, dialkylamino and $COOR^g$ wherein R^g is a (C_1-C_4)alkyl; and wherein W^3 is selected from

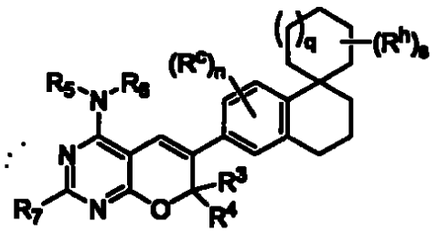


wherein R^i and R^j are each independently selected from H and (C_1-C_4)alkyl.

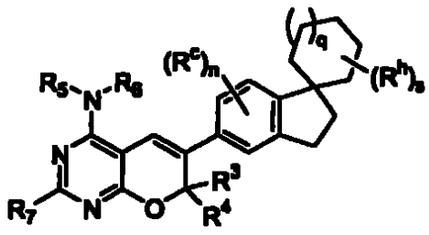
[0074] In still other groups of preferred embodiments, the compounds are represented by formulae Ir through Iy.



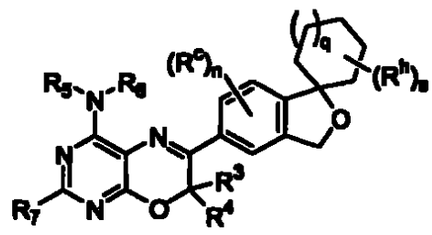
Ir



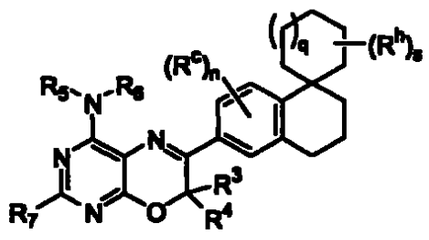
Is



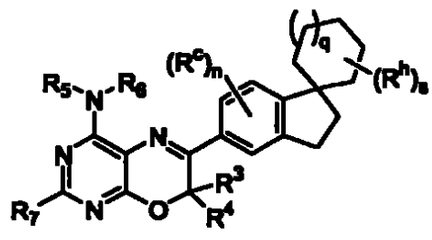
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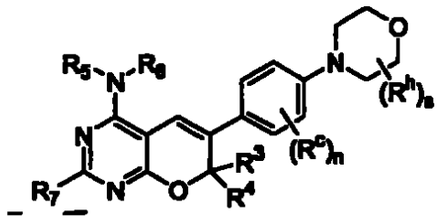
Iu



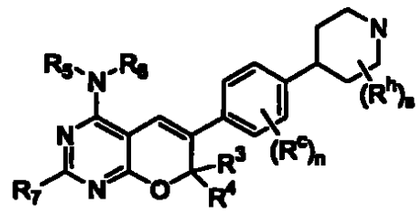
Iv



Iw



Ix

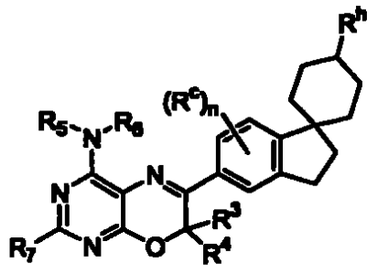


Iy

[0075] wherein each of R^3, R^4, R^5, R^6, $R^7$and R^c, as well as the subscript n have the meanings provided above with respect to formulae Ia-Ik. The subscript q is an integer of from 0 to 3, more preferably, 0 or 1. The subcript s is an integer of from 0 to 4, more preferably 0, 1 or 2, and each R^h is a substituent independently selected from the groups provided above for formulae II, Im, In, Io, Ip and Iq. Preferred groups for R^h are those provided above as preferred groups for formulae II, Im, In, Io, Ip and Iq.

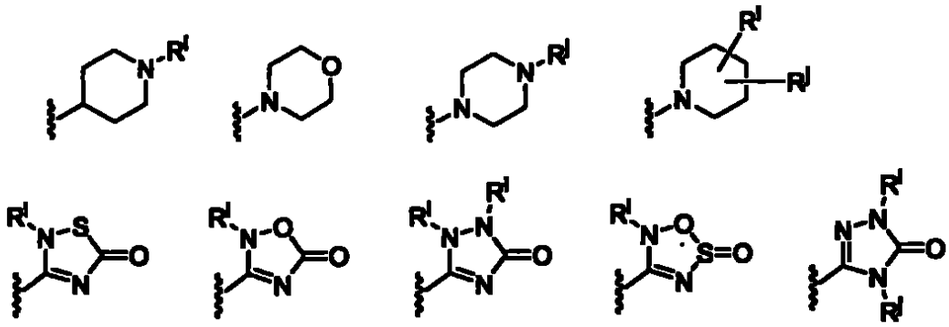
[0076] In preferred embodiments, R^3 and R^4 are each independently H, (C_1-C_4)alkyl or are combined to form a 3-, 4-, 5- or 6-membered spirocyclic ring; R^5 and R^6 are each H, (C_1-C_4)alkyl or are combined with the nitrogen to which each is attached to form a 5- or 6-membered ring (*e.g.* a pyrollidine or piperidine ring); and R^7 is H, (C_1-C_8)alkyl or halo(C_1-C_4)alkyl. Still further preferred are those embodiments in which the subscript n is 0, q is 1 and s is 1. In a particularly preferred group of embodiments, R^h represents a substituent having the formula $C(O)R^e$, CO_2R^e, $=CH\text{-}CO_2R^e$, $-CH_2\text{-}CO_2R^e$, $-CH(R^f)\text{-}CO_2R^e$, $-C(R^f)_2\text{-}CO_2R^e$, $-CH_2CH_2CO_2R^e$, $-C(O)NR^eR^f$, $=CH\text{-}CONR^eR^f$, $-CH_2C(O)NR^eR^f$, $-CH_2CH_2C(O)NR^eR^f$, $-CH_2CH_2NHCO_2R^e$, $-CH_2NHCO_2R^e$, $-NHSO_2R^e$, $-CH_2NHSO_2R^e$, $-CH_2CH_2NHSO_2R^e$, $-CH_2SO_2NR^eR^f$, $-CH_2CH_2SO_2NR^eR^f$, $-CH_2OH$, $-CH_2NR^eR^f$, $-CH_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2\text{-}W^3$, $-CH_2CH_2\text{-}W^3$, $-C(O)CO_2R^e$ or $-CH_2\text{-}C(CF_3)_2\text{-}OH$, wherein each R^e, R^f and W^3 is as described above.

[0077] In a particularly preferred group of embodiments, the compounds have the formula Iw.4 wherein the substituents have the meanings provided above with respect to general formula I, and are preferably selected from the preferred groups provided with respect to formulae Ir through Iy.



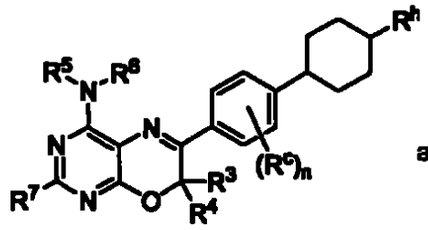
Iw.4

[0078] More preferably, the compounds of formula Iw.4 are those in which R^3 and R^4 are independently H or unsubstituted (C_1-C_4)alkyl; R^5 and R^6 are independently H or unsubstituted (C_1-C_4)alkyl; R^7 is selected from H, unsubstituted (C_1-C_4)alkyl or halo(C_1-C_4)alkyl; the subscript n is 0, 1 or 2 and R^c is selected from fluoro, chloro, bromo, cyano, methyl, trifluoromethyl and nitro; R^h is selected from CO_2R^e, =CH-CO_2R^e, -CH_2-CO_2R^e, -CH_2NHCOR^e, -$CH(R^f)$-CO_2R^e, -$C(R^f)_2$-CO_2R^e, -$CH_2CH_2CO_2R^e$, -$C(O)NR^eR^f$, =CH-$CONR^eR^f$, -$CH_2C(O)NR^eR^f$, -$CH_2CH_2C(O)NR^eR^f$, -$CH_2CH_2NHCO_2R^e$, -$CH_2NHCO_2R^e$, -$CH_2NR^eR^f$, -CH_2-W^3 and -CH_2CH_2-W^3; wherein each R^e and R^f is H or (C_1-C_4)alkyl optionally substituted with a member selected from OH, COOH, NH_2, $CONH_2$, phenyl, dialkylamino and $COOR^g$ wherein R^g is a (C_1-C_4)alkyl; and wherein W^3 is selected from

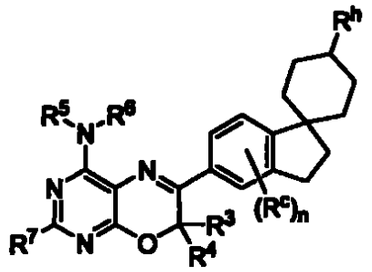


wherein R^i and R^j are each independently selected from H and unsubstituted (C_1-C_4)alkyl.

[0079] In other particularly preferred groups of embodiments, the compounds are represented by the formulae II.4 and Ig.4:



and

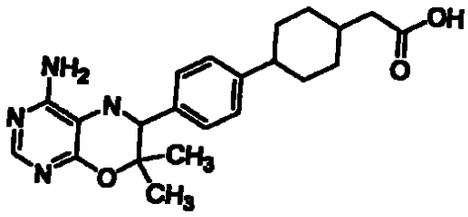


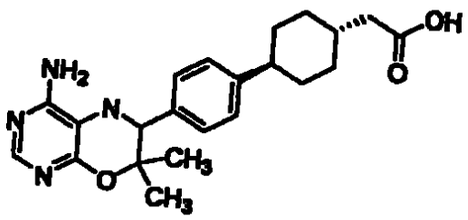
IL4 Ig.4

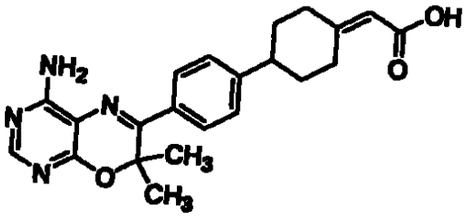
wherein each of the substituents have the meanings and preferred groups as provided above for formulae Ir through Iy.

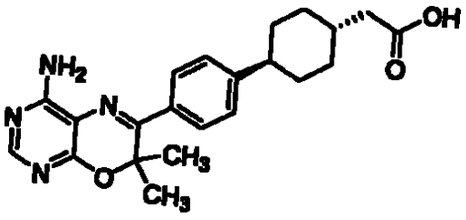
[0080] The more preferred compounds of the present invention are those that are provided in the examples below and further exemplified in Tables 1-10.

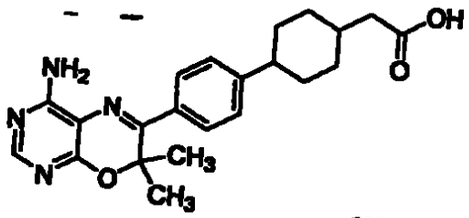
[0081] In one particularly preferred group of embodiments, the compounds are selected from:

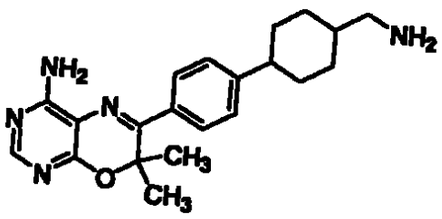


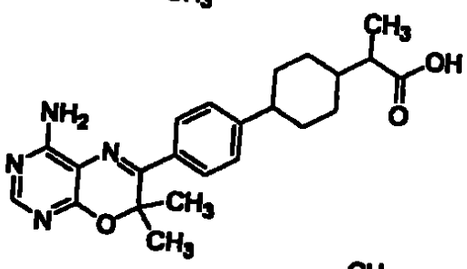


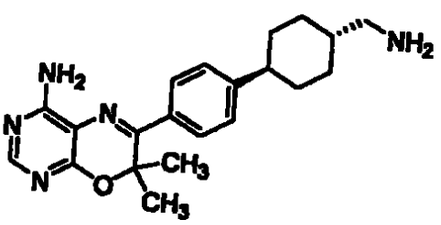


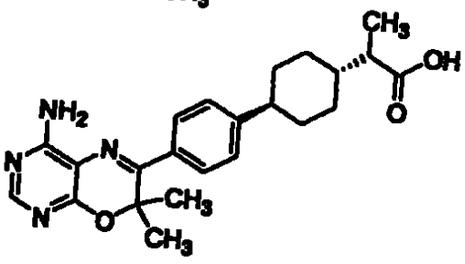


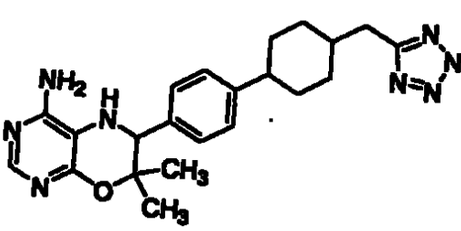


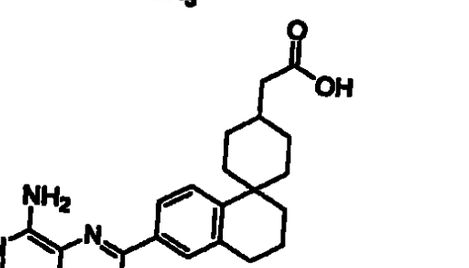


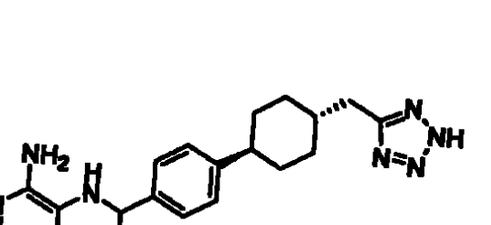


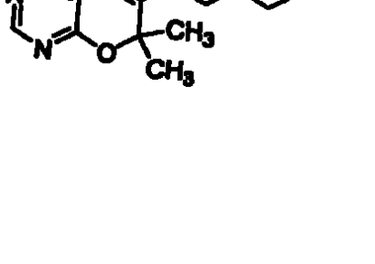


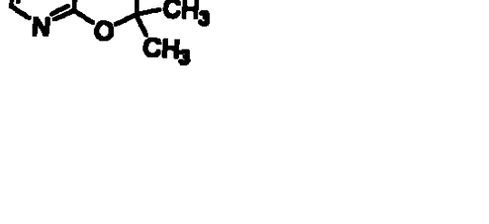


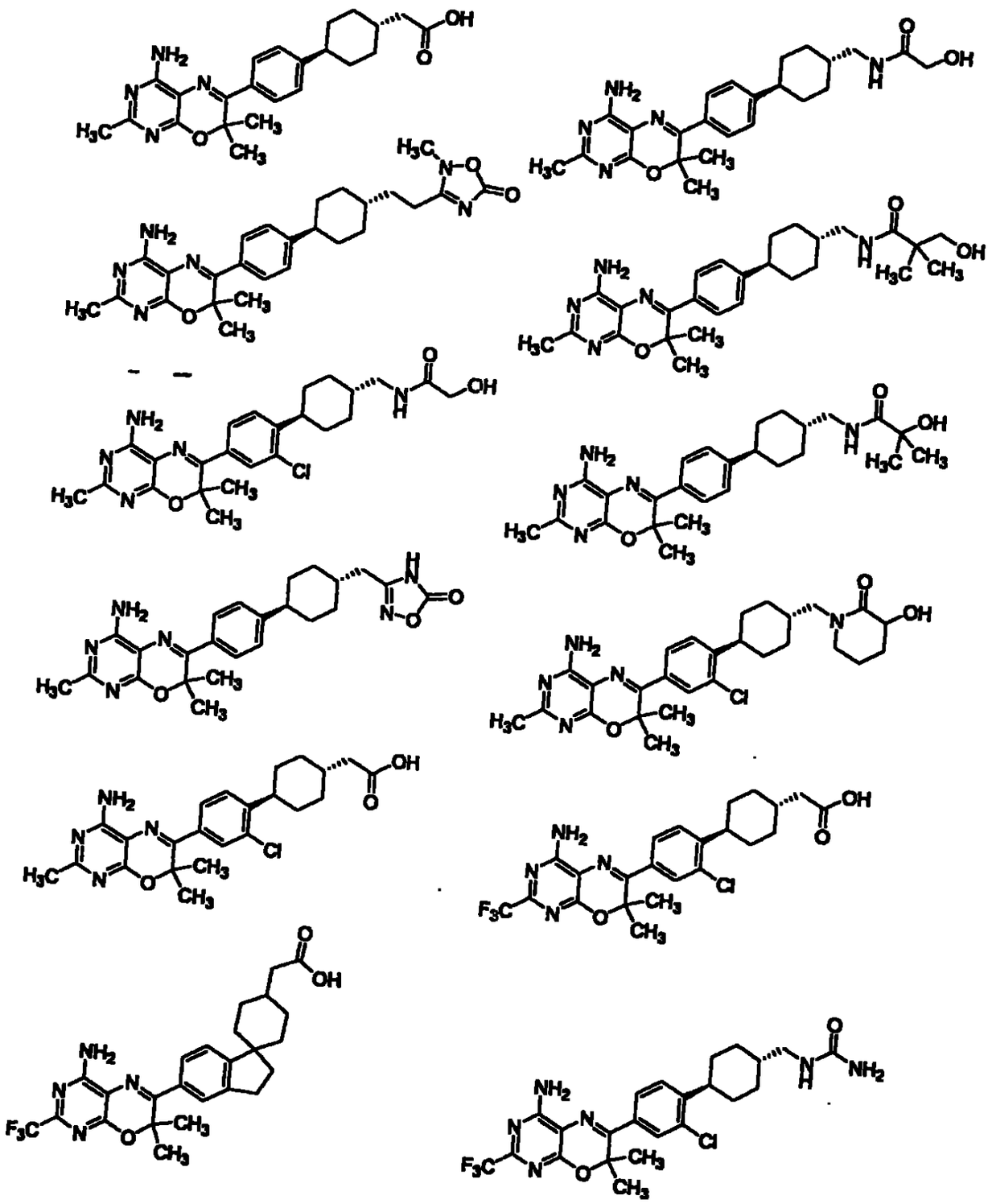


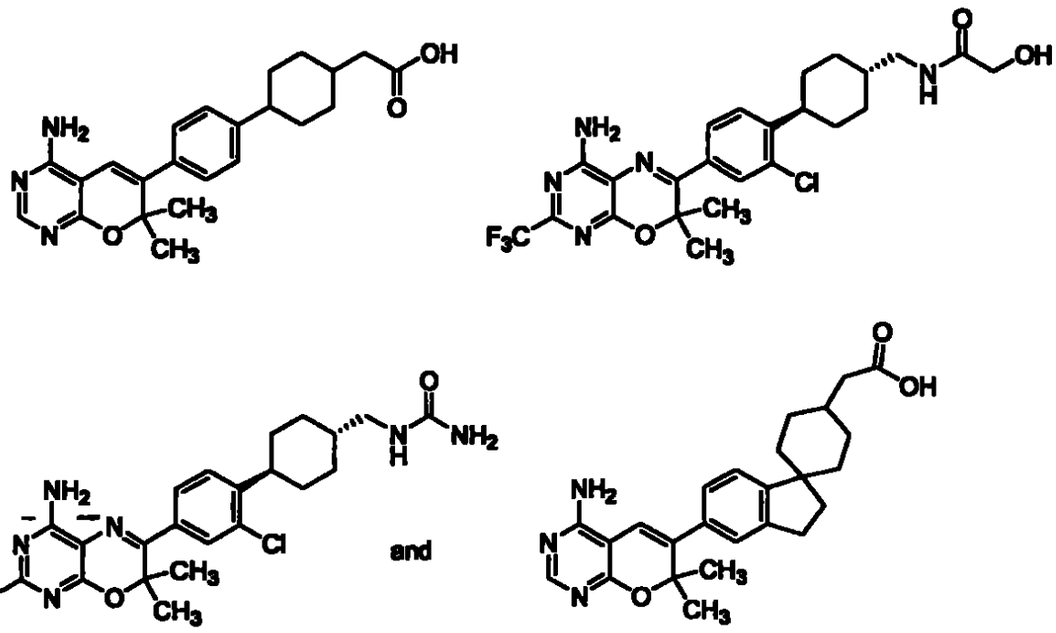








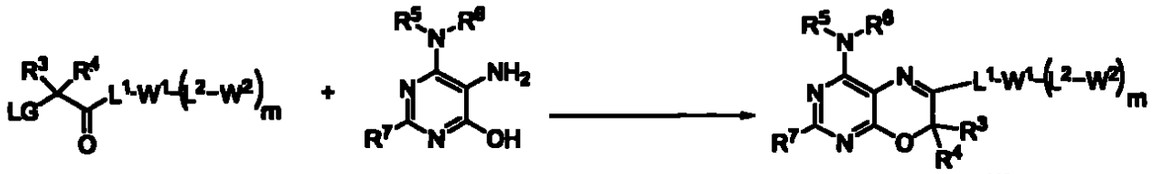




Preparation of compounds

[0082] Compounds of the present invention can be prepared beginning with commercially available starting materials and using general synthetic techniques known to those of skill in the art. Outlined below are reaction schemes suitable for preparing such compounds. Further exemplification is found in the specific Examples provided.

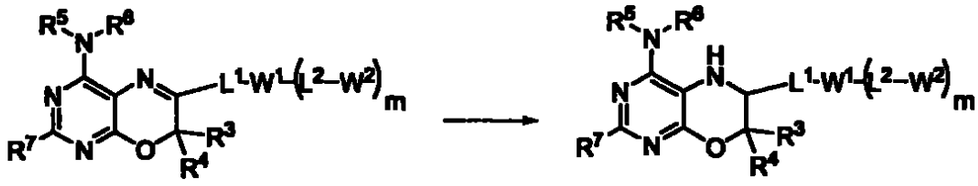
Scheme 1



i ii iii

[0083] As shown in Scheme 1, compounds of the present invention wherein X is N, Y is N and Z is O, can be prepared from a suitably substituted pyrimidine (ii) and a substituted ketone (i) wherein LG indicates a leaving group such as a halogen atom, toluenesulfonate, methanesulfonate or trifluoromethanesulfonate. Condensation of i and ii in an organic solvent or mixture of solvents (including aqueous mixtures) in the presence or absence of an acid (*e.g.*, HCl) or base (*e.g.*, $NaHCO_3$) provides, after workup, a compound of formula iii. Reduction of iii with a reducing agent such as, for example, sodium borohydride, lithium borohydride or sodium triacetoxyborohydride, provides still other compounds of the present invention, illustrated as iv in Scheme 2.

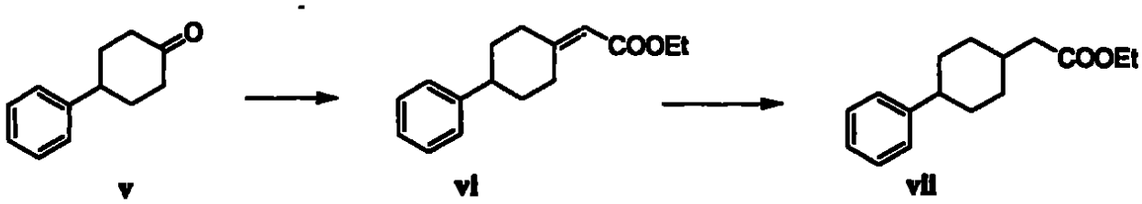
Scheme 2



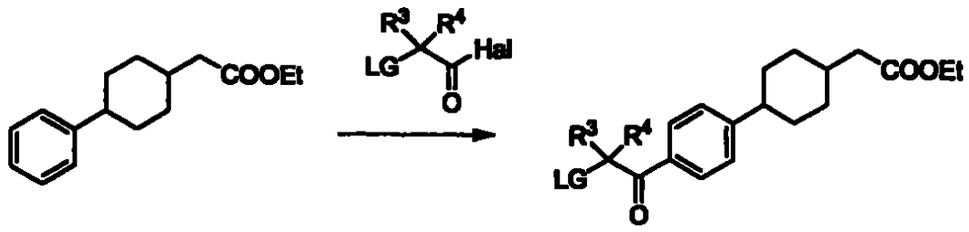
iii iv

[0084] Schemes 3a-3i illustrate a number of methods for the preparation of intermediate compounds of general structure i. In Scheme 3a, a benzene derivative, such as 4-phenyl-cyclohexanone (v), is functionalized to introduce a desired substituent on the cyclohexane ring. In the example shown, a Horner-Emmons or similar Wittig reaction is used to introduce an α,β -unsaturated ester group, producing vi (*e.g.*, reaction with a suitable phosphonate in the presence of a base such as sodium hydride in a solvent such as DMF or THF). Catalytic hydrogenation of vi using, for example, a palladium or platinum catalyst in a relatively polar solvent such as THF, methanol, or an aqueous mixture containing an alcohol or THF as a co-solvent, for example, is used to reduce the double bond, producing compound vii. A Friedel-Crafts acylation reaction is then used to attach a haloacetyl group on the phenyl ring of vii, forming the functionalized acetophenone (ix). Preferably, the leaving group in this sequence is Cl or Br. Suitable Lewis acids for the acylation include, for example, $AlCl_3$, $AlBr_3$, BCl_3, $TiCl_4$, and the like; suitable solvents are well known in the art, and include CS_2, nitrobenzene, dichloromethane, and similar solvents that are unreactive toward the reagents and Lewis acids employed. Those of skill in the art will appreciate that other synthesis methods are also known for making such intermediates, such as, for example, acylation of a metalated aromatic species, such as an aryllithium or aryl Grignard reagent, with, for example, an acylating agent such as an N-methyl-N-methoxy amide (commonly referred to as a Weinreb amide) of a chloroacetic acid derivative (*see, e.g.*, Nahm and Weinreb (1981) *Tetrahedron Lett.* 22:3815-3818) or a suitable acylester. Such methods provide access to other isomers of these functionalized acetophenone derivatives.

Scheme 3a



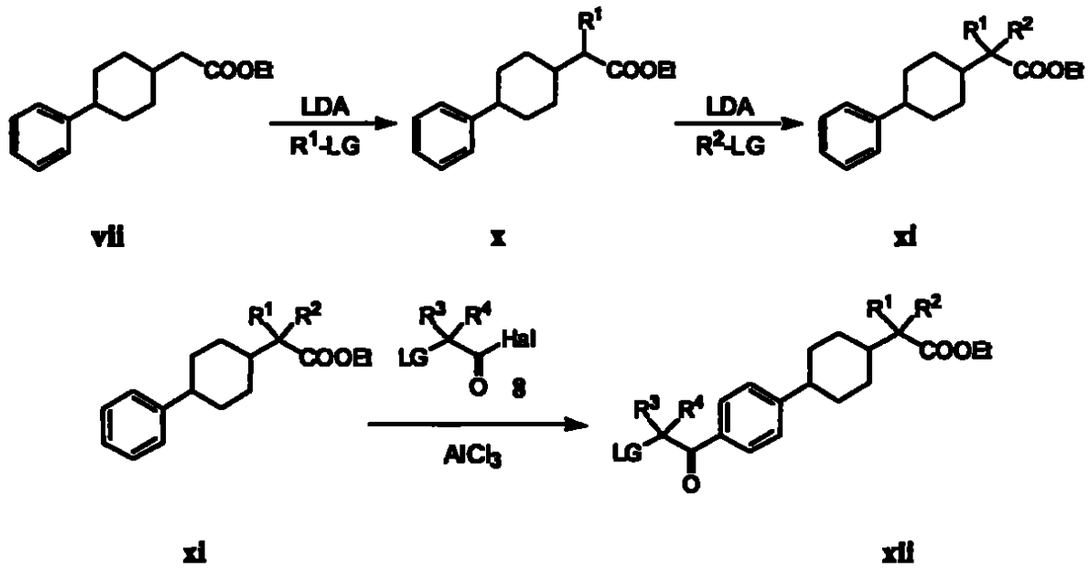
v vi vii



vii ix

[0085] Alternatively, vii may be alkylated by treatment with a base such as lithium diisopropylamide or lithium hexamethyldisilazide in a suitable solvent such as THF, followed by reaction with an alkylating agent, such as an alkyl halide, alkyl methanesulfonate, alkyl trifluoromethanesulfonate or alkyl toluenesulfonate, to give intermediate x (Scheme 3b). If desired, the sequence may be repeated to give intermediates of the general formula xi. Acylation of xi can be accomplished as described above to give xii.

Scheme 3b



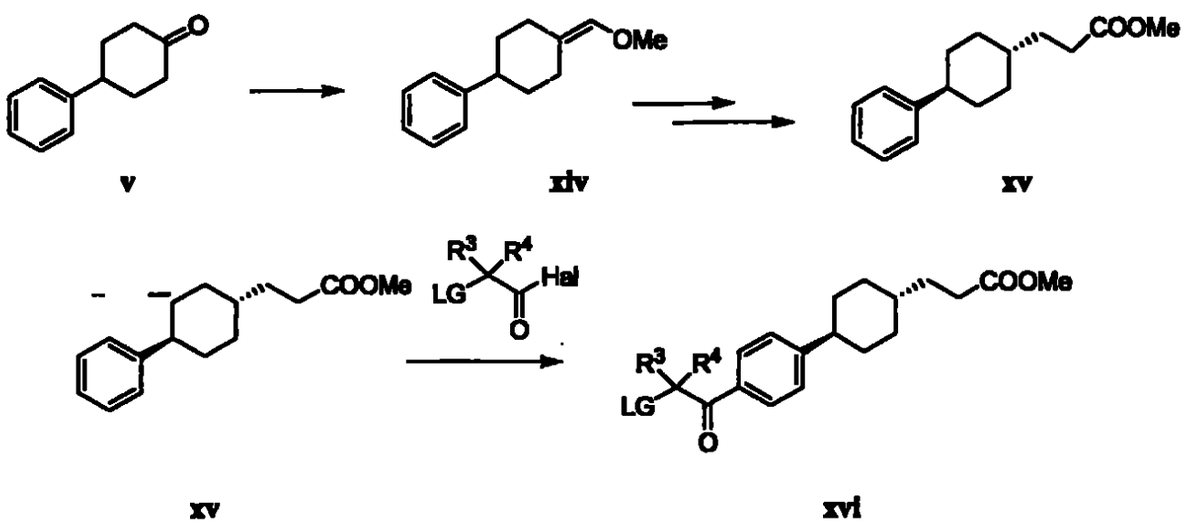
vii x xi

xi xii

[0086] Similar approaches can be used to produce other functionalized acetophenone derivatives (see Scheme 3c). For example, 4-phenylcyclohexanone (v) can be converted into an aldehyde in two steps, using a Wittig reaction with methoxymethyltriphenylphosphorane in a suitable solvent such as THF, DME or dioxane to produce xiv, for example, followed by mildly acidic hydrolysis. This aldehyde can be homologated into an α,β-unsaturated ester by a Wittig reaction with (carbomethoxy)methylenetriphenylphosphorane in a suitable solvent. If desired, the double bond can be reduced *via* catalytic hydrogenation using palladium on

carbon, for example, to produce xv. Suitable solvents for such hydrogenation reactions include ethanol or ethyl acetate. Acylation of xv to produce a functionalized acetophenone derivative (xvi) can be accomplished as described above for acylation of vii.

Scheme 3c

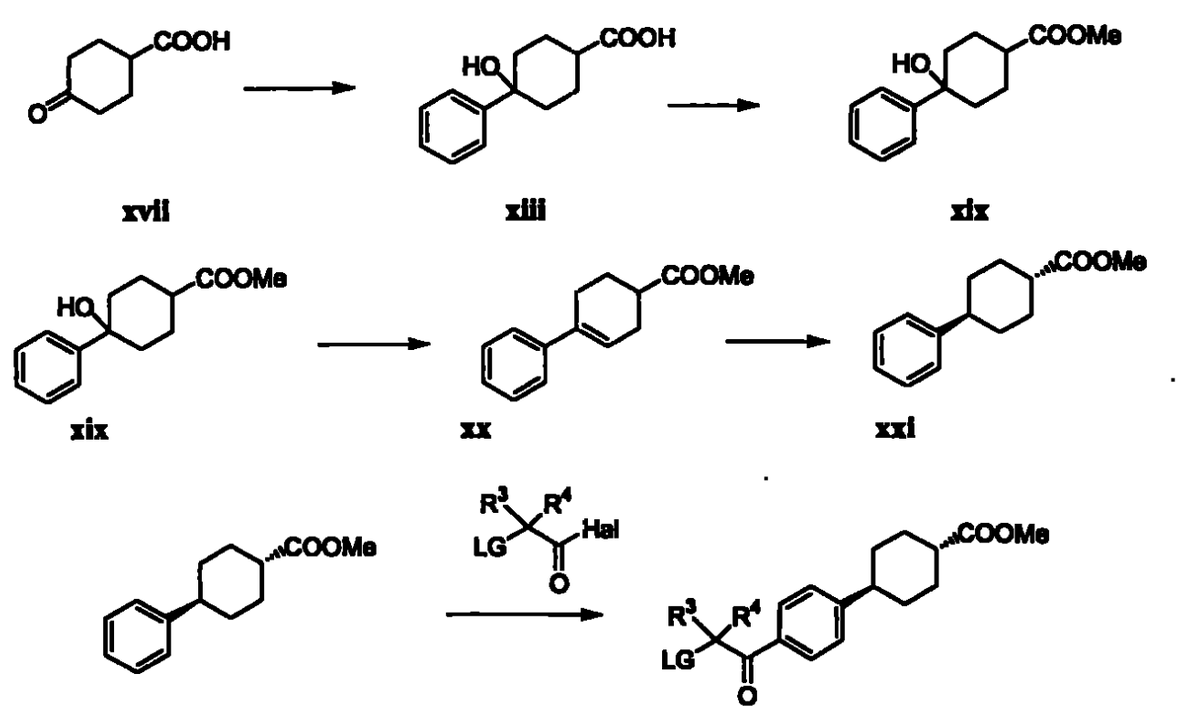


v xiv xv

xv xvi

[0087] Scheme 3d illustrates the synthesis of another functionalized acetophenone derivatives of general formula i, suitable for synthesizing compounds of the present invention.

Scheme 3d



xvii xiii xix

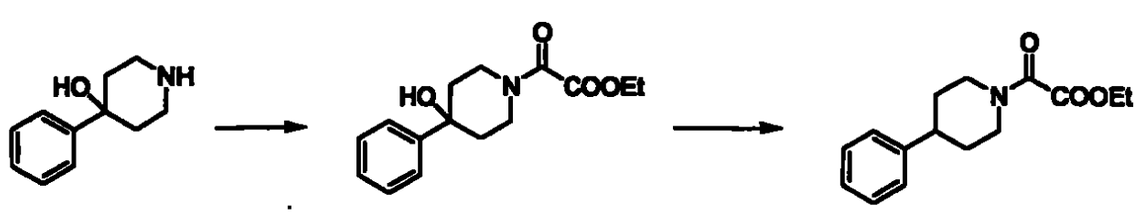
xix xx xxi

xxi xxii

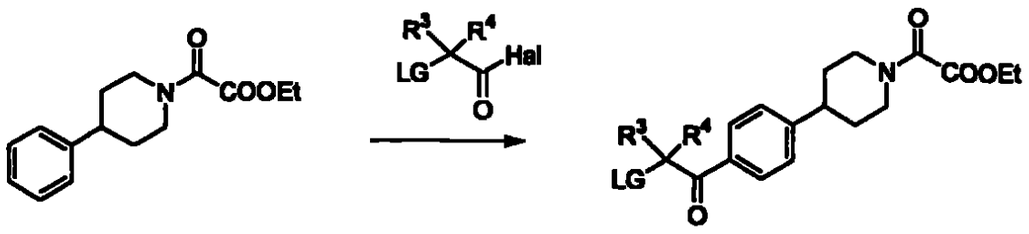
[0088] In Scheme 3d, a phenyl group is introduced using, for example, phenyl Grignard reagent or phenyllithium to provide xiii. The carboxylic acid functional group can be esterified under standard conditions to produce xix, and dehydration can be accomplished using an acid catalyst such as acetic acid, hydrochloric acid or trifluoroacetic acid in a suitable solvent such as chloroform or toluene to produce xx. Reduction of the cyclohexene double bond can be performed under catalytic hydrogenation conditions using palladium, typically, as the catalyst, to provide xxi. This reduction produces a mixture of isomers (both *cis* and *trans*-disubstituted cyclohexanes are produced); if desired, these can be separated or equilibrated using a base such as alkoxide or DBU in methanol or toluene to produce primarily the more thermodynamically stable *trans*-disubstituted isomer. Acylation of xxi to produce the functionalized acetophenone xxii is performed as described above.

[0089] Compounds of the present invention that contain a heterocyclic ring for W^2 can be synthesized by a similar sequence, provided the heterocyclic ring is stable to the acylation reaction conditions. For example, a compound where W^2 is an acylated piperidine can be synthesized in this manner, using a functionalized acetophenone derivative such as that produced by the sequence shown in Scheme 3e. In this sequence, 4-hydroxy-4-phenylpiperidine (xxiii) is alkylated, sulfonylated or acylated on nitrogen using reagents and conditions known to the skilled artisan (*e.g.*, acylation with diethyl oxalate or ethyl oxalyl chloride in the presence of a mild base such as triethylamine or pyridine) to produce xxiv. The N-functionalized (*e.g.*, N-acylated) compound is then dehydrated and reduced catalytically as described above in Scheme 3d to produce a 4-phenylpiperidine oxalate amide (xxv). This compound is then acylated as described above to produce the corresponding functionalized acetophenone derivatives (xxvi).

Scheme 3e



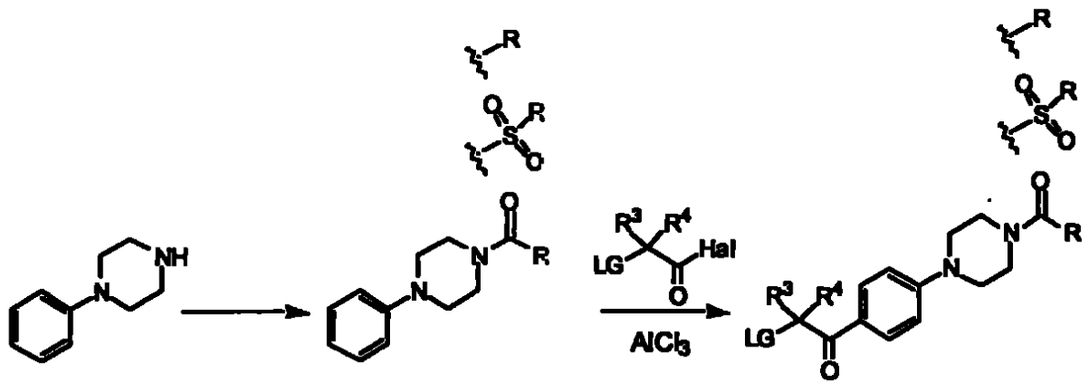
xxiii xxiv xxv



xxv xxvi

[0090] Similarly, the phenylpiperazine xxvii can be alkylated, sulfonylated, or acylated on nitrogen to give the N-functionalized compound xxviii, which can in turn be acylated as described previously to produce the functionalized acetophenone derivative xxix.

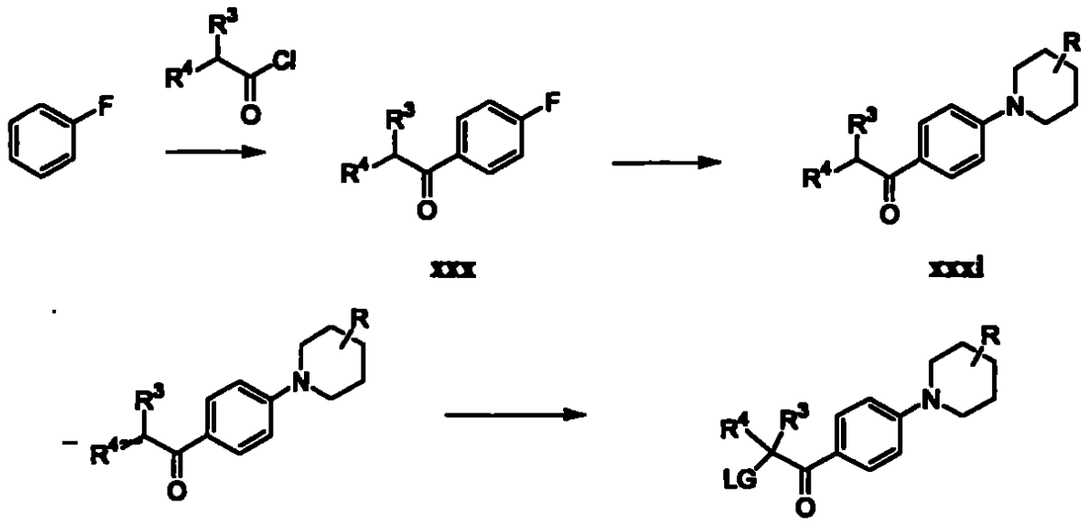
Scheme 3f



xxvii xxviii xxix

[0091] Other compounds of the present invention having a heterocycle as W^2 can be produced by attaching the heterocyclic group on an acetophenone, then halogenating the acetophenone at the α carbon to produce a compound of general formula I, as shown in Scheme 3g. In this sequence, a 4-fluoroacetophenone compound (xxiv) is synthesized by acylation of fluorobenzene under typical Friedel-Crafts conditions as described above. The 4-fluoro group is then subject to aromatic nucleophilic displacement reactions; in the scheme, it is displaced by a substituted piperidine group by reaction with the nucleophilic piperidine in a polar aprotic solvent such as DMSO or DMF. Functionalization of the carbon atom bearing R^3 and R^4 to produce xxvi can be accomplished using for example, bromine (Br_2) or chlorine (Cl_2) in a polar solvent such as DME or ethyl acetate, in the presence of an acid catalyst such as acetic acid or hydrobromic acid.

Scheme 3g

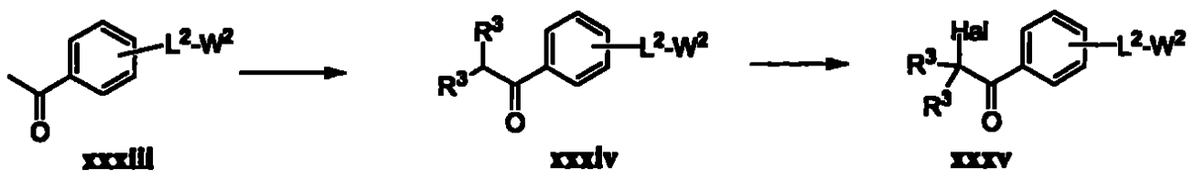


xxx xxxi

xxxi xxxii

[0092] Certain functionalized acetophenone derivatives suitable for the preparation of compounds of the present invention where L^1 is a bond can be prepared from substituted acetophenone, especially when R^3 and R^4 are identical groups, as shown in Scheme 3h. For example, an acetophenone substituted with $-L^2-W^2$ (xxxiii) can be alkylated with an alkylating agent such as methyl iodide, ethyl bromide, or other similar alkylating agent in the presence of a base such as lithium diisopropylamide, lithium hexamethyldisilazide or sodium hydride, and using a solvent such as DMF, DME, THF or toluene. This produces an acetophenone where R^3 and R^4 are the same. This acetophenone can then be halogenated as described above in Scheme 3g to produce a functionalized acetophenone of general formula I, which will condense with substituted pyrimidines as shown in Scheme 1 to prepare compounds of the present invention.

Scheme 3h

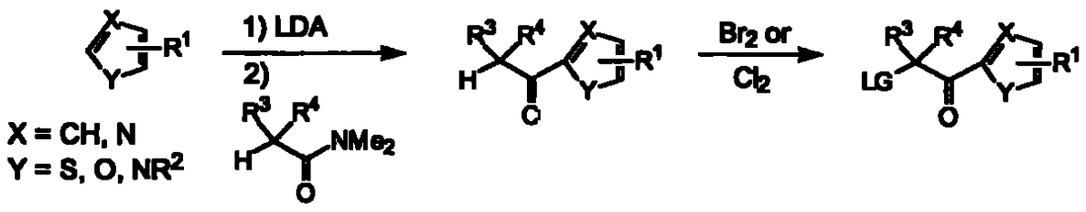


xxxiii xxxiv xxxv

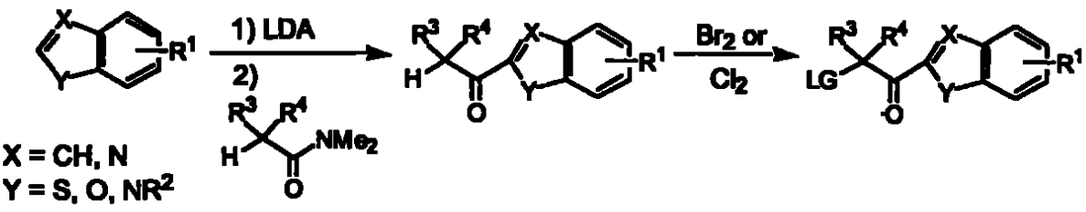
[0093] The preparation of compounds of the invention that contain a heterocyclic ring for W^1 can be synthesized using similar procedures, as outlined in Scheme 3g. For example, a substituted or unsubstituted heterocycle xxxvi such as a furan, thiophene, pyrrole, oxazole, thiazole, imidazole or thiadiazole can be lithiated with, for example butyllithium or lithium

diisopropyamide in a suitable solvent such as THF, DME or dioxane. The metalated species may be reacted with, for example, an amide, such as an dimethylamide or an N-methyl-N-methoxyamide to produce the acylated heterocycle xxxvii, which in turn can be halogenated as described above to produce a functionalized acetophenone derivative of general formula xxxviii. In a similar sequence, a substituted or unsubstituted benzofuran, benzothiophene, benzopyrrole, benzoxazole, benzothiazole, benzimidazole or benzothiadiazole (xxxix) can be lithiated and acylated to give xl, which in turn can be halogenated as previously described. One of skill in the art will appreciate that other heterocycles can also be used in these transformations.

Scheme 3i



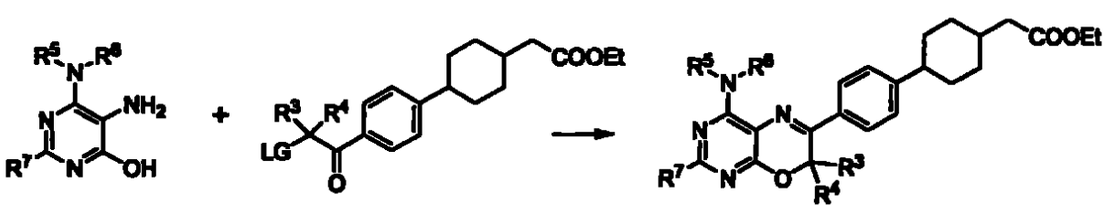
xxxvi xxxvii xxxviii



xxxix xl xli

[0094] As shown in Scheme 4, compounds of general formula iv having a substituted phenyl ring as W1 and a substituted cyclohexane ring as L2-W2 (e.g., xlii) can be prepared from these substituted acetophenone derivatives like ix.

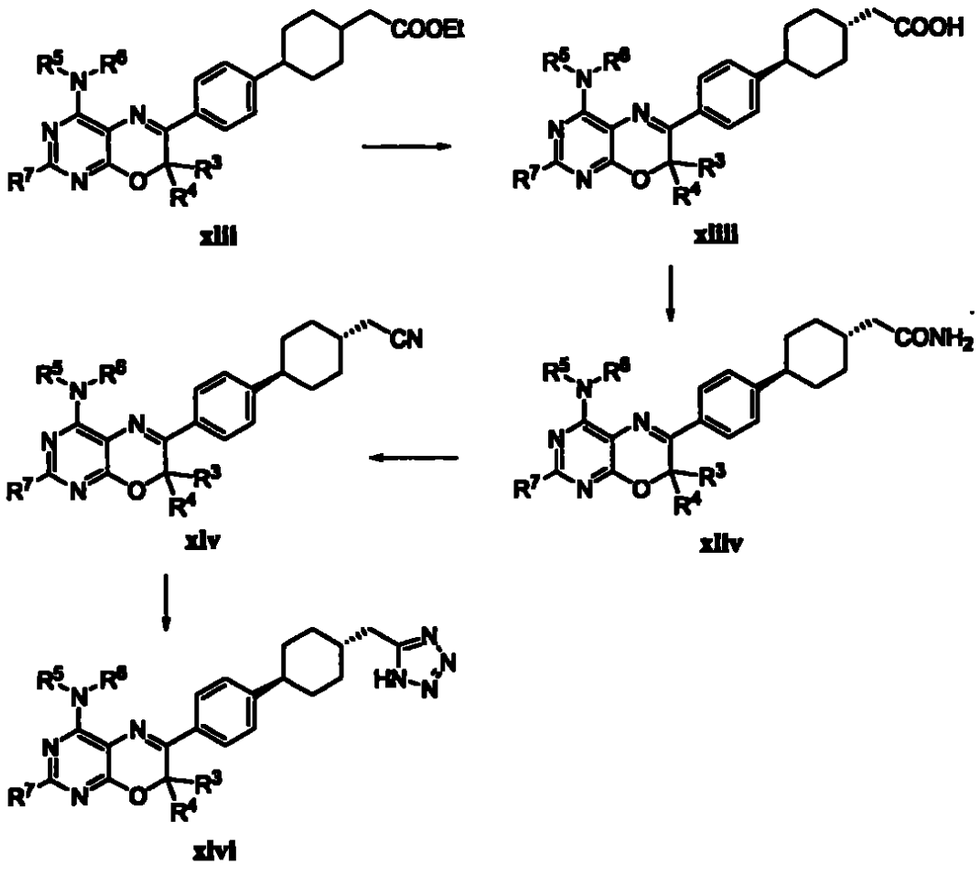
Scheme 4



ii ix xlii

[0095] Compounds such as xlii can be used to make other compounds of the present invention by, for example, hydrolysis of the ethyl ester to provide a carboxylic acid compound xliii. (Scheme 5) Ester hydrolysis can be accomplished in most solvents that will dissolve xlii and are at least partially miscible with water, by treating a solution of xlii with aqueous base such as sodium hydroxide or potassium hydroxide, for example. The carboxylic acid can, in turn, be converted into other groups such as an amide by methods well known to those of ordinary skill in the art. For example, the carboxylic acid can be activated by condensation with a variety of coupling reagents, including hydroxybenzotriazole (HOBt) and N-hydroxysuccinimide (HOSu), for example, using dicyclohexylcarbodiimide (DCC) or a similar carbodiimide reagent or a wide variety of reagents such as those developed for formation of peptide bonds. Conditions for such reactions are well known to those or ordinary skill in the art. The activated intermediate, an ester of HOBt or HOSu, for example, can then be condensed with a wide variety of nucleophiles such as, for example, amines, alcohols, and thiols. Scheme 5 shows the conversion of a compound of formula xlii into an amide (xliv) by this sequence, using ammonia as the nucleophile.

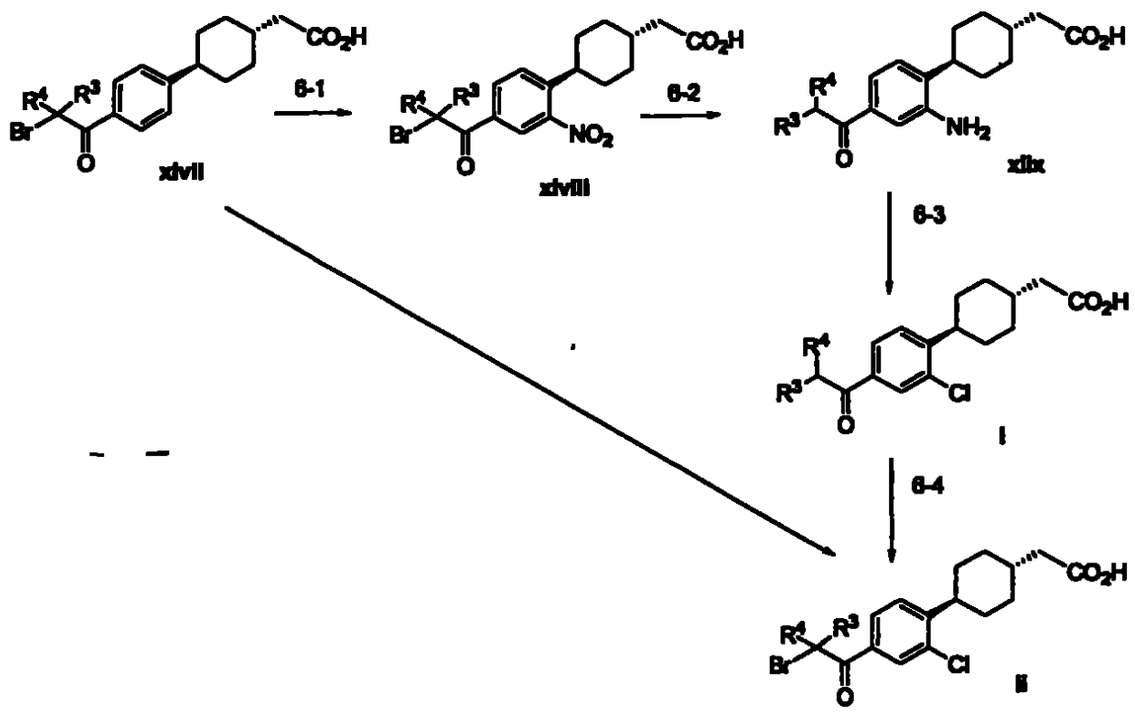
Scheme 5



[0096] Dehydration of the amide xliv to a nitrile (xlv) can be accomplished by a variety of methods. *See* Scheme 5 above. Phosphorous pentoxide is the most common dehydrating reagent for this reaction, but many others are known to those skilled in the art. The nitrile can, in turn, be converted into other groups such as a tetrazole (xlvi) by methods well known to those of ordinary skill in the art. For example, reacting the nitrile with an azide, such as sodium azide, lithium azide or hydrazoic acid in a solvent such as DMF or water will accomplish this transformation.

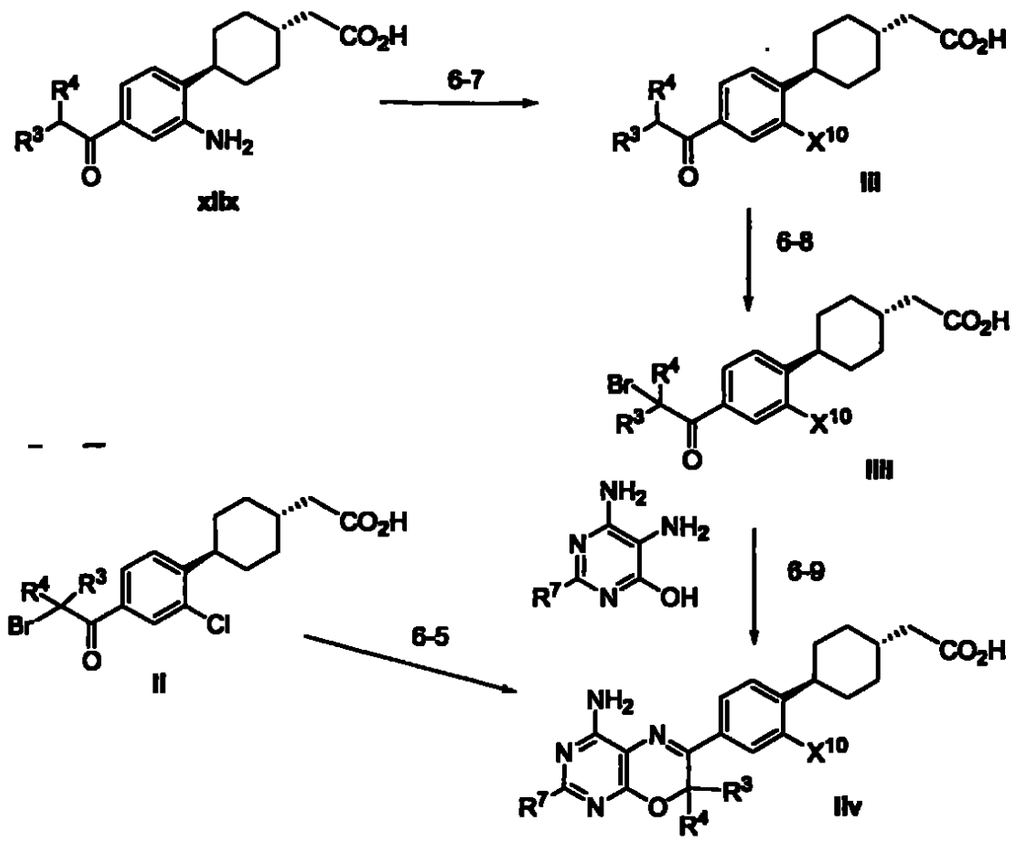
[0097] Schemes 6a and 6b illustrate one approach to the preparation of compounds of formula I in which W^1 is a phenylene moiety having an additional substituents other than the L^2-W^2 component. As seen in Scheme 6a, intermediate bromoacetophenones xlvii can be nitrated under standard conditions (nitric acid, sulfuric acid in solvents such as chloroform, methylene chloride, acetic acid, or neat) to provide xlviii. Reduction of the nitro group is accompanied by debromination to provide xlix using catalytic hydrogentation or $SnCl_2$ (generally in alcoholic solvents). Chloride replacement of the amino group is accomplished using copper chloride in the presence of a suitable nitrite (e.g., t-butyl nitrite, sodium nitrite) and solvent, to provide intermediates such as l. Bromine can be reintroduced, providing li using standard brominating conditions (e.g., HBr/HOAc, Br_2/N-bromosuccinimide or $CuBr_2$). Alternatively, xlvii can be chlorinated directly to provide li using standard reagents (e.g., sulfuryl chloride, Cl_2 or N-chlorosuccinimide) and conditions known to one of skill in the art.

Scheme 6a



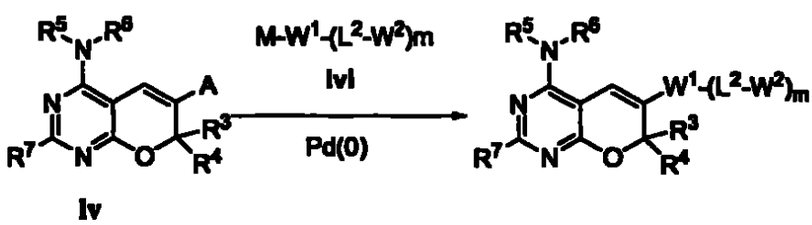
[0098] Scheme 6b illustrates the elaboration of intermediates such as xlix to other substituted compounds. For example, compounds of formula lii (wherein X^{10} is F) can be produced from xlix using fluorinating reagents such as nitrosonium tetrafluoroborate, DAST, HF or CsF (generally in solvents such as toluene, benzene, methylene chloride or dichloroethane). Subsequent bromination of lii to produce liii can be accomplished according to known methods. Conversion of either li or liii to target compounds of the formula liv is accomplished via condensation with a suitably substituted pyrimidine (see Example 1).

Scheme 6b



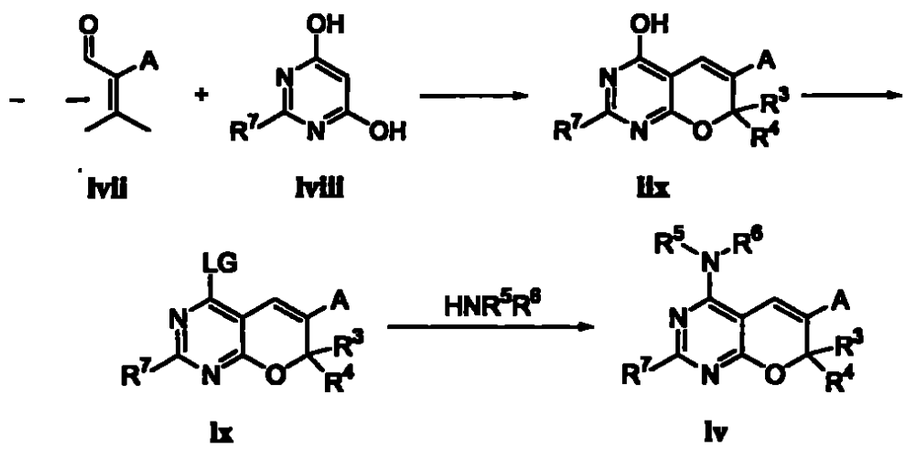
[0099] As shown in Scheme 7, compounds of the present invention wherein X is N, Y is CH, Z is O and W^1 is a substituted or unsubstituted aryl or heteroaryl can be prepared from a suitably substituted pyrimidine Iv (where A is a halogen, *e.g.*, Br, I or a triflate or other suitable substituent known to those skilled in the art) and a substituted or unsubstituted aryl or heteroaryl species Ivi (where M is $B(OR^2)$, $Sn(R^3)$ or other suitable metal known to those skilled in the art) by, for example, a palladium catalyzed cross coupling reaction. Those skilled in the art will also appreciate that A and M may be interchanged.

Scheme 7



[0100] Scheme 8 illustrates a method for the preparation of the intermediate of general structure Iv. Condensation of pyrimidine Ivlll with Ivll in a suitable solvent such as acetic acid affords IIx. Conversion of the hydroxy moiety to a leaving group, for example, a chloride or bromide with, for example, phosphorus oxychloride or phosphorus oxybromide respectively, is followed by displacement of the leaving group with a suitably substituted amine to afford Iv.

Scheme 8



Compositions

[0101] In another aspect, the present invention provides pharmaceutical compositions for modulating DGAT activity in humans and animals that will typically contain a compound of formula I and a pharmaceutically acceptable carrier or diluent.

[0102] The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases.

aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0106] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0107] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0108] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[0109] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

[0110] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be

[0103] The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with other non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

[0104] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[0105] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxy-ethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The

employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0111] The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[0112] For topical use, patches, creams, ointments, jellies, solutions or suspensions, *etc.*, containing the compounds of the present invention are employed. As used herein, topical application is also meant to include the use of mouth washes and gargles.

[0113] The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above-mentioned pathological conditions.

Methods of Use

[0114] In yet another aspect, the present invention provides methods of using a compound or composition of the invention to treat or prevent a disease or condition associated with DGAT. Diseases and conditions associated with lipid metabolism and cell proliferation, and complications thereof, can be treated with the subject compounds and compositions. In one group of embodiments, diseases and conditions, including chronic diseases, of humans or other species that can be treated with inhibitors of DGAT function include, but are not limited to, metabolic disorders, such as obesity, diabetes, anorexia nervosa, bulimia, cachexia, syndrome X, insulin resistance, hypoglycemia, hyperglycemia, hyperuricemia, hyperinsulinemia, hypercholesterolemia, hyperlipidemia, dyslipidemia, mixed dyslipidemia, hypertriglyceridemia and nonalcoholic fatty liver disease; cardiovascular diseases, such as atherosclerosis, arteriosclerosis, acute heart failure, congestive heart failure, coronary artery disease, cardiomyopathy, myocardial infarction, angina pectoris, hypertension, hypotension, stroke, ischemia, ischemic reperfusion injury, aneurysm, restenosis and vascular stenosis; neoplastic diseases, such as solid tumors, skin cancer, melanoma, lymphoma and endothelial cancers, *e.g.*, breast cancer, lung cancer, colorectal cancer, stomach cancer, other cancers of the gastrointestinal tract (*e.g.*, esophageal cancer and pancreatic cancer), prostate cancer,

kidney cancer, liver cancer, bladder cancer, cervical cancer, uterine cancer, testicular cancer and ovarian cancer; and other diseases and conditions that are sensitive or responsive to modulation of DGAT function.

[0115] The methods of the present invention typically involve administering to a subject in need of therapeutic treatment, an effective amount of a compound of formula (I). The dose, frequency and timing of such administering will depend in large part on the selected therapeutic agent, the nature of the condition being treated, the condition of the subject including age, weight and presence of other conditions or disorders, the formulation being administered and the discretion of the attending physician. Preferably, the compositions and compounds of the invention and the pharmaceutically acceptable salts thereof are administered *via* oral, parenteral or topical routes. Generally, the compounds are administered in dosages ranging from about 2 mg up to about 2,000 mg per day, although variations will necessarily occur depending, as noted above, on the disease target, the patient, and the route of administration. Preferred dosages are administered orally in the range of about 0.05 mg/kg to about 20 mg/kg, more preferably in the range of about 0.05 mg/kg to about 2 mg/kg, most preferably in the range of about 0.05 mg/kg to about 0.2 mg per kg of body weight per day. The dosage employed for the topical administration will, of course, depend on the size of the area being treated.

Combination therapy with additional active agents

[0116] The present invention further provides methods of using a compound or composition of the invention in combination with one or more additional active agents, depending on the desired target therapy (*see, e.g.*, Turner, N. *et al. Prog. Drug Res.* (1998) 51: 33-94; Haffner, S. *Diabetes Care* (1998) 21: 160-178; and DeFronzo, R. *et al.* (eds.), *Diabetes Reviews* (1997) Vol. 5 No. 4). A number of studies have investigated the benefits of combination therapies with oral agents (*see, e.g.*, Mahler, R., *J. Clin. Endocrinol. Metab.* (1999) 84: 1165-71; United Kingdom Prospective Diabetes Study Group: UKPDS 28, *Diabetes Care* (1998) 21: 87-92; Bardin, C. W.,(ed.), CURRENT THERAPY IN ENDOCRIN LOGY AND METABOLISM, 6th Edition (Mosby - Year Book, Inc., St. Louis, MO 1997); Chiasson, J. *et al.*, *Ann. Intern. Med.* (1994) 121: 928-935; Coniff, R. *et al.*, *Clin. Ther.* (1997) 19: 16-26; Coniff, R. *et al.*, *Am. J. Med.* (1995) 98: 443-451; and Iwamoto, Y. *et al.*, *Diabet. Med.* (1996) 13 365-370; Kwiterovich, P. *Am. J. Cardiol* (1998) 82 (12A): 3U-17U).

[0117] In particular, the studies provided above indicate that diabetes and hyperlipidemia modulation can be further improved in many instances by the addition of a second agent to the therapeutic regimen. Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound having the general structure of formula I and one or more additional active agents, as well as administration of a compound of formula I and each active agent in its own separate pharmaceutical dosage formulation. For example, a compound of formula I and an HMG-CoA reductase inhibitor can be administered to the human subject together in a single oral dosage composition, such as a tablet or capsule, or each agent can be administered in separate oral dosage formulations. Where separate dosage formulations are used, a compound of formula I and one or more additional active agents can be administered at essentially the same time (*i.e.*, concurrently), or at separately staggered times (*i.e.*, sequentially). Combination therapy is understood to include all these regimens.

[0118] An example of combination therapy that modulates (prevents the onset of the symptoms or complications associated with) atherosclerosis involves administering a compound of formula I in combination with one or more of the following active agents: an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent, such as a cholesterol biosynthesis inhibitor, *e.g.*, an hydroxymethylglutaryl (HMG) CoA reductase inhibitor (also referred to as statins, such as lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin), an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, or a squalene synthetase inhibitor (also known as squalene synthase inhibitor); an acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitor, such as melinamide; probucol; nicotinic acid and the salts thereof and niacinamide; a cholesterol absorption inhibitor, such as β-sitosterol; a bile acid sequestrant anion exchange resin, such as cholestyramine, colestipol or dialkylaminoalkyl derivatives of a cross-linked dextran; an LDL (low density lipoprotein) receptor inducer; fibrates, such as clofibrate, bezafibrate, fenofibrate, and gemfibrizol; vitamin B_6 (also known as pyridoxine) and pharmaceutically acceptable salts thereof, such as the HCl salt; vitamin B_{12} (also known as cyanocobalamin); vitamin B_3 (also known as nicotinic acid and niacinamide, *supra*); anti-oxidant vitamins, such as vitamin C and E and beta carotene; a beta-blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; and a platelet aggregation inhibitor, such as fibrinogen receptor antagonists (*i.e.*, glycoprotein IIb/IIIa fibrinogen receptor antagonists) and aspirin. As noted above, the compounds of formula I can be administered in combination

with more than one additional active agent, for example, a combination of a compound of formula I with an HMG-CoA reductase inhibitor (*e.g.*, lovastatin, simvastatin and pravastatin) and aspirin, or a compound of formula I with an HMG-CoA reductase inhibitor and a β blocker.

[0119] Another example of combination therapy can be seen in treating obesity or obesity-related disorders, wherein the compounds of formula I can be effectively used in combination with, for example, phenylpropanolamine, phentermine, diethylpropion, mazindol; fenfluramine, dexfenfluramine, phentiramine, β_3 adrenoceptor agonist agents; sibutramine, gastrointestinal lipase inhibitors (such as orlistat), and leptins. Other agents used in treating obesity-or obesity-related disorders can be used in combination with compounds of formula I including, for example, neuropeptide Y, enterostatin, cholecytokinin, bombesin, amylin, histamine H_3 receptors, dopamine D_2 receptors, melanocyte stimulating hormone, corticotrophin releasing factor, galanin and gamma amino butyric acid (GABA).

[0120] Another example of combination therapy can be seen in modulating diabetes (or treating diabetes and its related symptoms, complications, and disorders), wherein the compounds of formula I can be effectively used in combination with, for example, sulfonylureas (such as chlorpropamide, tolbutamide, acetohexamide, tolazamide, glyburide, gliclazide, glynase, glimepiride, and glipizide), biguanides (such as metformin), thiazolidinediones (such as ciglitazone, pioglitazone, troglitazone, and rosiglitazone); dehydroepiandrosterone (also referred to as DHEA or its conjugated sulphate ester, DHEA-SO_4); antiglucocorticoids; TNFα inhibitors; α-glucosidase inhibitors (such as acarbose, miglitol, and voglibose), pramlintide (a synthetic analog of the human hormone amylin), other insulin secretogogues (such as repaglinide, gliquidone, and nateglinide), insulin, as well as the active agents discussed above for treating atherosclerosis.

[0121] Still another example of combination therapy can be seen in modulating hyperlipidemia (treating hyperlipidemia and its related complications), wherein the compounds of formula I can be effectively used in combination with, for example, statins (such as fluvastatin, lovastatin, pravastatin or simvastatin), bile acid-binding resins (such as colestipol or cholestyramine), nicotinic acid, probucol, betacarotene, vitamin E, or vitamin C.

[0122] In accordance with the present invention, a therapeutically effective amount of a compound of formula I can be used for the preparation of a pharmaceutical composition useful for treating diabetes, treating hyperlipidemia, treating hyperuricemia, treating obesity,

lowering triglyceride levels, lowering cholesterol levels, raising the plasma level of high density lipoprotein, and for treating, preventing or reducing the risk of developing atherosclerosis.

[0123] A further example of combination therapy can be seen in modulating dermatological conditions, wherein compounds of formula I can be effectively used in combination with, for example, acne treatments (*e.g.*, isotretinoin, doxycycline, tetracycline, salicylate) and seborrheic dermatitis treatments (antifungal agents such as climbazole, ketoconazole). Moreover, compounds of formula I can be effectively used to enhance the transdermal delivery of drugs applied topically in the form of a patch, lotion, jellies, cream, *etc.*

[0124] Still another example of combination therapy can be seen in treating nonalcoholic fatty liver disease (NAFLD), wherein compounds of formula I can be effectively used in combination with hepatoprotective agents such as ursodeoxycholic acid and betaine.

[0125] Additionally, an effective amount of a compound of formula I and a therapeutically effective amount of one or more active agents selected from the group consisting of: an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent, such as a cholesterol biosynthesis inhibitor, for example, an HMG-CoA reductase inhibitor, an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, or a squalene synthetase inhibitor (also known as squalene synthase inhibitor); an acyl-coenzyme A cholesterol acyltransferase inhibitor; probucol; nicotinic acid and the salts thereof; niacinamide; a cholesterol absorption inhibitor; a bile acid sequestrant anion exchange resin; a low density lipoprotein receptor inducer; clofibrate, fenofibrate, and gemfibrozil; vitamin B_6 and the pharmaceutically acceptable salts thereof; vitamin B_{12}; an anti-oxidant vitamin; a β -blocker; an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; a platelet aggregation inhibitor; a fibrinogen receptor antagonist; aspirin; phentiramines, β_3 adrenergic receptor agonists; sulfonylureas, biguanides, α-glucosidase inhibitors, other insulin secretogogues, insulin and a hepatoprotective agent can be used together for the preparation of a pharmaceutical composition useful for the above-described treatments.

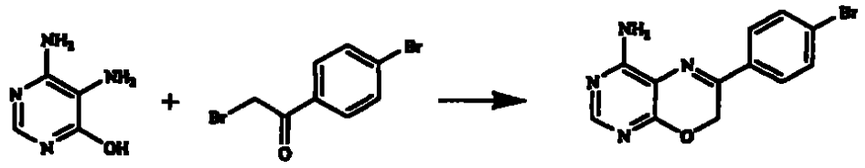
EXAMPLES

[0126] ^{1}H-NMR spectra were recorded on a Varian Gemini 400 MHz, Jeol Alpha 300 MHz, Bruker DPX 300 MHz, Varian Mercury 400 MHz or Bruker Avance 500 MHz NMR spectrometer. Significant peaks are tabulated and typically include: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet) and

coupling constant(s) in Hertz. IR spectra were recorded on a Perkin Elmer 1600 FT-IR or a Perkin Elmer Spectrum One FT-IR. Mass spectrometry results are reported as the ratio of mass over charge, followed by the relative abundance of each ion (in parentheses). Starting materials in the synthesis examples below are either available from commercial sources such as Aldrich Chemical Co., Milwaukee, Wisconsin, USA, or *via* literature procedures. Abbreviations used in the examples below have their accepted meanings in the chemical literature. For example, THF (tetrahydrofuran), Et_2O (diethyl ether), MeOH (methanol), LDA (lithium diisopropylamide), MeCN (acetonitrile), DMAP (4-dimethyaminopyridine), WSC (1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide), HOBt (1-hydroxybenzotriazole), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DME (1,2-dimethoxyethane), DMF (*N,N*-dimethylformamide), DMSO (dimethyl sulfoxide), AcOH (acetic acid) and AcOEt (ethyl acetate). Other conventional abbreviations are used herein: for example, a methyl group is often provided as an unlabeled terminal "bond", according to accepted practice.

Example 1

[0127] This example illustrates the preparation of the compound designated Ex. 1.



Ex. 1

[0128] To a suspension of 4,5-diamino-6-hydroxypyrimidine (1.0 g, 7.93 mmol) and 4-bromophenacyl bromide (2.2 g, 7.93 mmol) in EtOH (20 mL) was added $NaHCO_3$ (666 mg, 7.93 mmol), and the mixture was stirred for 1.5 h at 80 °C. After cooling, the reaction mixture was concentrated, and the residue was diluted with $CHCl_3$ (40 mL). After filtration of insoluble material, the filtrate was concentrated. The residue was triturated with toluene to give the desired compound Ex. 1 (840 mg) as a pale yellow crystal, m.p.: >200 °C. IR (cm^{-1}): 3291, 3145, 1634, 1586. MS (ESI+): 305, 307 (100). 1H NMR (DMSO-d6, 400 MHz): 5.44 (s, 2H), 7.10 (br s, 2H), 7.69 (d, 2H, J = 8.6 Hz), 7.93 (s, 1H), 8.03 (d, 2H, J = 8.6 Hz).

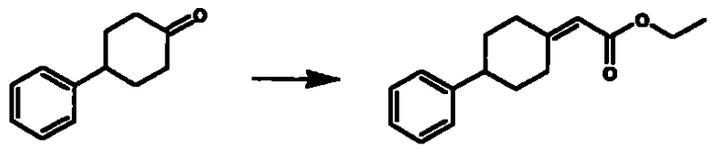
Example 1-2 to 1-37:

[0129] The compounds shown in Table 1 were obtained in the same manner as in Example 1.

Example 2

[0130] This example illustrates the preparation of the compound designated Ex. 2.

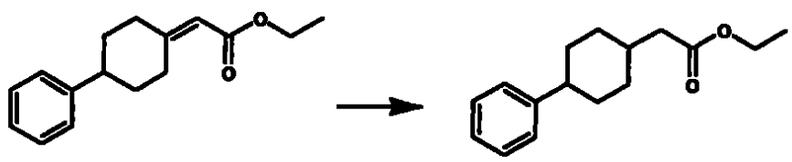
a)



1 2

[0131] At 0 °C, to a solution of triethyl phosphonoacetate (2.6 mL, 12.91 mmol) in DMF(5.5 mL), sodium hydride(60% in oil, 517 mg, 12.91 mmol) was added portionwise, and the reaction mixture was stirred at room temperature for 30 min. A solution of 4-phenylcyclohexanone in DMF (2.0 mL) was added. After stirring for 0.5 h, the mixture was poured into 5% aq. $KHSO_4$ (10 mL) and extracted with diethyl ether (10 mL). The organic layer was successively washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (hexane/AcOEt=7/1) to give compound 2 (2.0 g) as colorless oil.

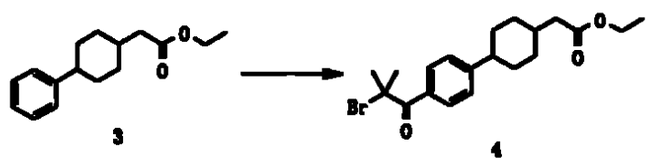
b)



2 3

[0132] To a stirred solution of 2 (500 mg, 2.05 mmol) in EtOH (5 mL) was added 10% Pd/C (50 mg). The mixture was stirred at room temperature for 1 h under an atmospheric pressure of hydrogen. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to afford crude compound 3 (491 mg) as colorless oil, which was used for the next reaction without further purification.

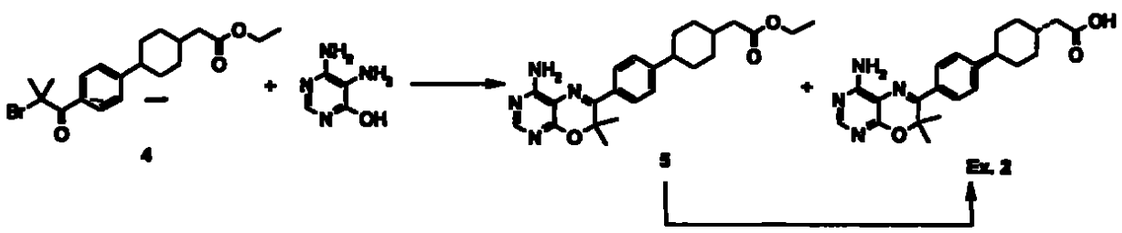
c)



3 4

[0133] At 0 °C, to a solution of compound 3 (271 mg, 1.10 mmol) in CH_2Cl_2 (1.4 mL), anhydrous $AlCl_3$ (440 mg, 3.30 mmol) was added portionwise and then 2-bromoisobutyryl bromide (0.14 mL, 1.10 mmol) was added dropwise. After stirring for 1h at 0 °C, the mixture was poured into ice water and extracted with $CHCl_3$ (5 mL). The combined organic layer was successively washed with sat. $NaHCO_3$ (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (hexane/AcOEt=7/1) to give compound 4 (402 mg) as colorless oil.

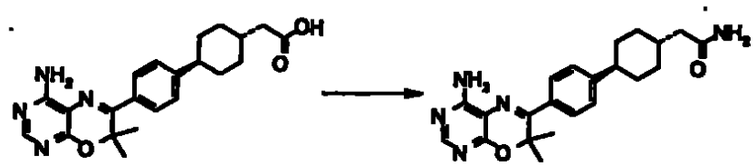
d)



[0134] 4,5-Diamino-6-hydroxypyrimidine (63.1 mg, 0.50 mmol) was mixed with 1N HCl aq. (0.50 mL, 0.50 mmol), water (2 mL) and EtOH (2 mL) and compound 4 (395 mg, 1.00 mmol) in EtOH (2 mL). The reaction mixture was refluxed (105 °C) for 12 h. The reaction mixture was concentrated to half amount of volume. The residue was adjusted to pH 9-10 with 2N NaOH aq. The resulting mixture was extracted with AcOEt (5 mL). The aqueous layer was adjusted to pH 3-4 with 10% citric acid aq., extracted with AcOEt (5 mL). The organic layer was washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$. Evaporation of the solvent gave a crude Ex. 2 (54 mg, mixture of *cis* and *trans* isomers). The first organic layer was washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$. Evaporation of the solvent gave a crude compound 5 (126 mg, mixture of *cis* and *trans* isomers), which was used for the next reaction without further purification. To a solution of crude compound 5 in EtOH (1.2 mL), THF (1.8 mL) and water (1.2 mL) was added 2N NaOH aq. (0.45 mL) after stirring at 40°C for 4 h. The reaction mixture was concentrated to half amount of volume, and added to water (2 mL) and washed with AcOEt (2 mL). The aqueous layer was adjusted to pH 3-4 with 10% citric acid aq., and extracted with AcOEt (5 mL). The organic layer was washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$. Evaporation of the solvent gave a white solid (113 mg). The white solid (113 mg) and crude Ex. 2 (54 mg) were combined and recrystallized from EtOH to give Ex. 2 (92 mg, *trans* isomer), as a white crystal, m.p.: >270 °C. IR (cm^{-1}): 3320, 2929, 1702, 1601. MS (ESI+): 395 (100). 1H NMR (DMSO-d6, 300 MHz): 1.10-1.16 (m, 2H), 1.45-1.84 (m, 13H), 2.15

(d, 2H, J=6.0Hz), 2.54 (m, 1H), 6.97 (br s, 2H), 7.30 (d, 2H, J=8.4Hz), 7.64 (d, 2H, J=8.4Hz), 7.94 (s, 1H), 11.95 (br s, 1H).

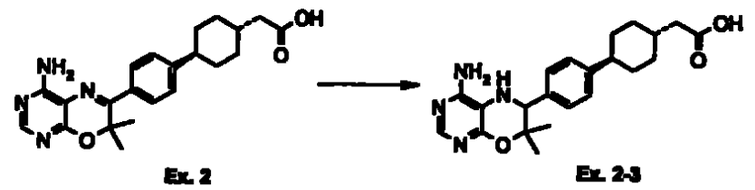
Example 2-2:



Ex. 2 Ex. 2-2

[0135] To a solution of Ex. 2 (80 mg, 0.20 mmol) in DMF (2.4 mL) was added HOBt-H_2O (34.2 mg, 0.22 mmol), EDC-HCl (42.8 mg, 0.22 mmol) and 28% ammonia aq. (0.04 mL, 0.81 mmol). The reaction mixture was stirred at room temperature for 70 h. The mixture was poured into sat. $NaHCO_3$ aq. and extracted with AcOEt (3 mL). The organic layer was successively washed with water (3 mLx2), sat. $NaHCO_3$ (3 mL) and brine (3 mL), dried over $MgSO_4$. Evaporation of the solvent gave a white solid (69.5 mg). The solid was slurried with EtOH to give compound Ex. 2-2 (48.2 mg) as a white crystal, m.p.: 224-226 °C. IR (cm^{-1}): 3348, 2923, 1672, 1604. MS (ESI+): 394 (100). 1H NMR (DMSO-d6, 400 MHz): 1.03-1.22 (m, 8H), 1.4-1.49 (m, 2H), 1.70-1.82 (m, 5H), 2.14 (d, 2H, J=6.9Hz), 2.54 (m, 1H), 4.11 (br s, 1H), 5.27 (br s, 1H), 6.23 (br s, 2H), 7.25 (d, 2H, J=8.0Hz), 7.36 (d, 2H, J=8.0Hz), 7.61 (s, 1H), 11.75 (br s, 1H).

Example 2-3:



Ex. 2 Ex. 2-3

[0136] At 0 °C, to a solution of Ex. 2 (120 mg, 0.30mmol) in THF (3.6 mL) and MeOH (3.6 mL), $NaBH_4$ (194 mg, 4.86 mmol) was added portionwise and the reaction mixture was stirred at 0 °C for 20 h. 2N NaOH aq. (0.46 mL, 0.91 mmol) was added and stirred for 30 min at 60 °C. The reaction mixture was concentrated to half amount of volume. The residue was added to water (3 mL) and washed with AcOEt (3 mL). The aqueous layer was adjusted to pH 3-4 with 10% citric acid aq., extracted with AcOEt (5 mL). The organic layer was washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$. Evaporation of the solvent gave a white solid (150 mg). The solid was recrystallized from EtOH to give Ex. 2-3 (97 mg)

as a white crystal, m.p.: 274-279 °C (decomposed). IR (cm^{-1}): 3414, 2927, 1650, 1595. MS (ESI+): 397 (100). 1H NMR (DMSO-d6, 300 MHz): 1.02-1.17 (m, 2H), 1.40-1.53 (m, 2H), 1.61 (s, 6H), 1.66-1.87 (m, 5H), 1.98 (d, 2H, J=7.1Hz), 2.53 (m, 1H), 6.67 (br s, 1H), 6.89 (br s, 2H), 7.21 (br s, 1H), 7.30 (d, 2H, J=8.1Hz), 7.63 (d, 2H, J=8.1Hz), 7.94 (s, 1H).

Example 2-4:

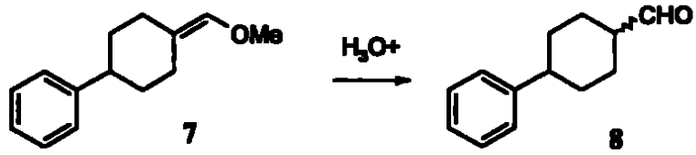
a)



1 7

[0137] To a stirred suspension of methoxymethyltriphenylphosphonium chloride (3.14 g, 9.2 mmol) in THF (8 mL) was added potassium tert-butoxide (516 mg, 4.6 mmol) under Ar. After 1 h, 4-phenylcyclohexanone (1) (400 mg, 2.3 mmol) was added to the solution. The mixture was stirred for 1 h at room temperature, heated overnight at 70 °C. After cooling, the reaction mixture was poured into sat. $NaHCO_3$ (40 mL) and extracted with ether (50 mL). The organic extract was washed with water (40 mL) and brine (40 mL) and dried over Na_2SO_4, and the solvent was removed to give crude compound 7 (2.19 g), which was used to the next step without further purification.

b)



7 8

[0138] The crude compound 7 (2.19 g) was mixed with 80% aq. AcOH (25 mL) and heated at 70 °C for 3.5 h with stirring. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (hexane/AcOEt=20/1) to give compound 8 (395 mg) as colorless oil.

c)

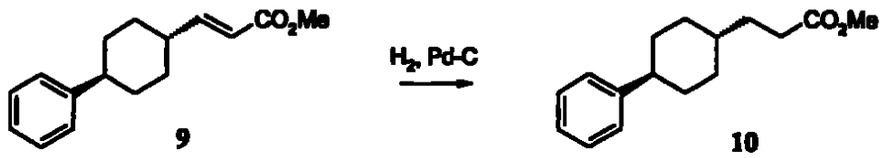


8 9

[0139] To a stirred solution of compound 8 (383 mg, 2.03 mmol) in toluene (20 mL) was added DBU (365 μL, 2.44 mmol) and the mixture was heated at 80°C for 5 h under Ar. Then to the reaction mixture was added methyl (triphenylphosphoranylidene) acetate (1.2 g, 3.05 mmol) and the mixture was stirred overnight at 100 °C. After cooling, the reaction mixture

was washed with 5%$KHSO_4$ (10 mL), sat. $NaHCO_3$ (10 mL) and brine (10 mL), and the organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (hexane/AcOEt=20/1) to give compound 9 (474 mg) as colorless oil.

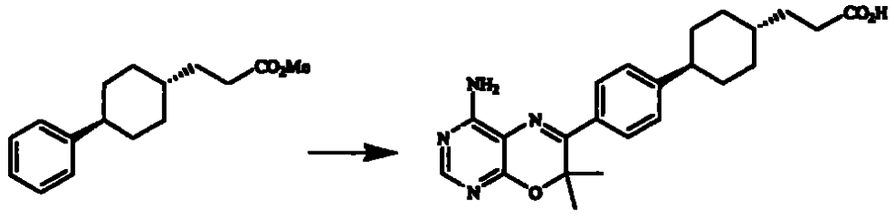
d)



9 10

[0140] A suspension of 10% palladium on charcoal (50 mg) in a solution of compound 9 (474 mg, 1.94 mmol) in EtOH (15 mL) was hydrogenated under the atmospheric pressure of a hydrogen atmosphere overnight at room temperature. The reaction mixture was filtered, and the filtrate was concentrated to give compound 10 (436 mg) as colorless oil, which was pure enough to be used for the next step without further purification.

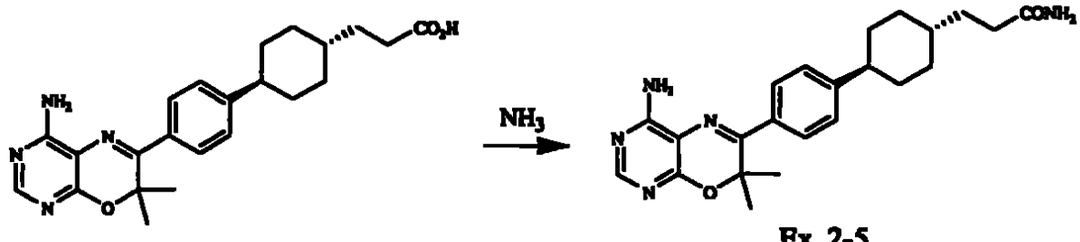
e)



10 Ex. 2-4

[0141] The Example 2 procedure was applied to compound 10 on a 436 mg (1.94 mmol) scale, yielding Ex. 2-4 (231 mg) as a colorless crystal, m.p.: >250 °C. IR (cm^{-1}): 3310, 2922, 1702, 1611. MS (ESI+): 409 (100). 1H NMR (DMSO-d6, 400 MHz): 1.04-1.09 (m, 2H), 1.43 (m, 1H), 1.43-1.50 (m, 4H), 1.60 (s, 6H), 1.83 (br d, 4H, J=11.4 Hz), 2.25 (t, 2H, d=7.7 Hz), 2.50 (m, 1H), 6.88 (br s, 2H), 7.29 (d, 2H, J=8.3 Hz), 7.63 (d, 2H, J=8.3 Hz), 7.94 (s, 1H), 11.84 (br s, 1H).

Example 2-5:

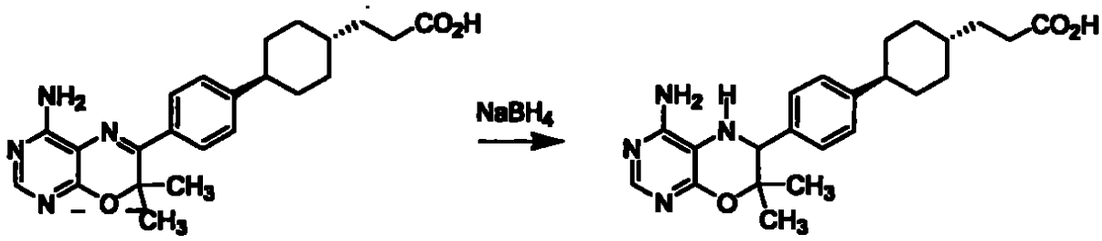


Ex. 2-4 Ex. 2-5

[0142] The Example 2-2 procedure was applied to Ex. 2-4 on a 50 mg (0.12 mmol) scale, yielding Ex. 2-5 (41 mg) as a colorless crystal, m.p.: 244-246 °C. IR (cm^{-1}): 3357,

2920, 1696, 1602. MS (ESI+): 408 (100). 1H NMR (DMSO-d6, 400 MHz): 1.04-1.08 (m, 2H), 1.29 (m, 1H), 1.40-1.49 (m, 4H), 1.60 (s, 6H), 1.83 (br d, 4H, J=10.2 Hz), 2.09 (t, 2H, d=7.4 Hz), 2.50 (m, 1H), 6.60 (br s, 1H), 6.88 (br s, 2H), 7.20 (br s, 1H), 7.29 (d, 2H, J=8.3 Hz), 7.63 (d, 2H, J=8.3 Hz), 7.94 (s, 1H).

Example 2-6:



Ex. 2-4 Ex. 2-6

[0143] The Example 2-3 procedure was applied to Ex. 2-4 on a 38 mg (0.09 mmol) scale, yielding Ex. 2-6 (19 mg) as a colorless crystal, m.p.: >250 °C. IR (cm^{-1}): 3348, 2922, 1638, 1595. MS (ESI+): 411 (100). 1H NMR (DMSO-d6, 400 MHz): 1.04-1.09 (m, 2H), 1.08 (s, 3H), 1.22 (s, 3H), 1.32 (m, 1H), 1.43-1.48 (m, 4H), 1.83 (br d, 4H, J=10.7 Hz), 2.24 (t, 2H, d=7.7 Hz), 2.50 (m, 1H), 4.11 (s, 1H), 5.26 (s, 1H), 6.22 (br s, 2H), 7.23 (d, 2H, J=8.1 Hz), 7.35 (d, 2H, J=8.1 Hz), 7.62 (s, 1H), 11.73 (br s, 1H).

Example 2-7:

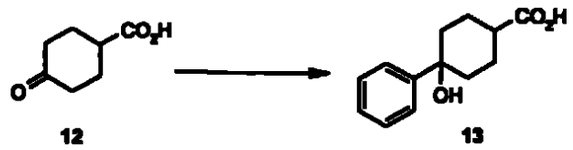
a)



11 12

[0144] Compound 11 (3 mL, 18.82 mmol) and 30 mL of ethanol and NaOH solution were stirred together at room temperature for 3 h. Solvents were then removed *in vacuo*, and 12 mL of 2M HCl solution was added. The aqueous layer was extracted with 25 mL of AcOEt, and the extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford crude compound 12, which was used for the next reaction without further purification.

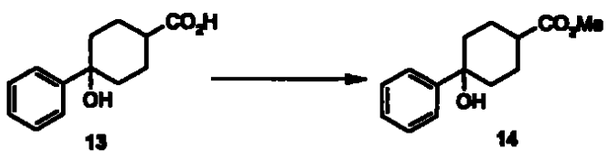
b)



12 13

[0145] To a stirred solution of crude compound 12 (1.594 g, ca. 11.21 mmol) in 15 mL of THF was added 1.0M PhMgBr (24.7 mL, 24.7 mmol) at 0 °C and stirred for 30 min. After addition of 10 mL of water, the mixture was acidified with 1M HCl solution. The aqueous layer was extracted with 30 mL of AcOEt, and the extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford crude compound 13, which was used for the next reaction without further purification.

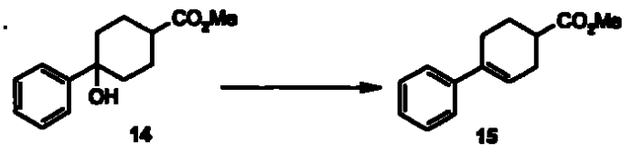
c)



13 14

[0146] To a stirred suspension of crude compound 13 and K_2CO_3 (2.01 g, 14.5 mmol) in 10 mL of DMF was added MeI (0.98 mL, 15.7 mmol) and stirred for 3 h. After addition of 15 mL of water, the aqueous layer was extracted with 25 mL of AcOEt, and the extract was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to afford crude compound 14, which was used for the next reaction without further purification.

d)



14 15

[0147] Crude compound 14, 15 mL of $CHCl_3$, trifluoroacetic acid (3.02 mL, 39.4 mmol) and triethylsilane (3.02 mL, 22.5 mmol) were stirred together at 65 °C for 5.5 h. After addition of 25 mL of water, the organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt=10/1) to give compound 15 (1.5 g) as pale yellow oil.

e)



15 16

[0148] To a stirred solution of compound 15 (1.5 g, 6.94 mmol) in 15 mL of MeOH was added 10% Pd/C (240 mg). The mixture was stirred at room temperature for 5 h under an atmospheric pressure of hydrogen. The catalyst was removed by filtration, and filtrate was concentrated in vacuo to afford crude compound 16, which was used for the next reaction without further purification.

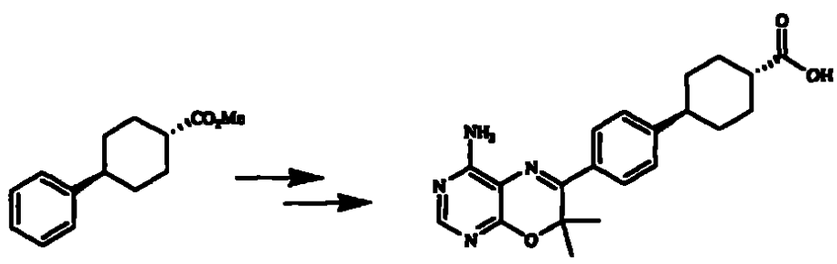
f)



16 17

[0149] Crude compound 16 and 10 mL of MeOH and 28%MeONa (1.5 mL, 7.3 mmol, methanol solution) were stirred together at 70 °C for 7.5 h. After addition of 30 mL of water, the aqueous layer was extracted with 40 mL of AcOEt, and the extract was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to afford crude compound 17 as a mixture of diastereomers (ratio 4:1), which was used for the next reaction without further purification.

g)



17 Ex. 2-7

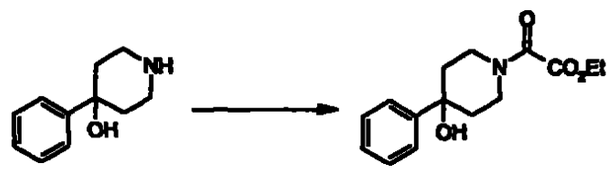
[0150] The Example 2-c) and 2-d) procedure was applied to compound 17 on a 69 mg (0.55 mmol) scale, yielding Ex. 2-7 (54 mg) as a colorless crystal, m.p.: >250 °C. IR (cm^{-1}): 3328, 2931, 1704, 1615. MS (ESI+): 381 (100). 1H NMR (DMSO-d6, 400 MHz): 1.40-1.58 (m, 4H), 1.61 (s, 6H), 1.82-1.92 (m, 2H), 1.97-2.08 (m, 2H), 2.24-2.36 (m, 1H), 2.52-2.61 (m, 1H), 6.91 (br s, 2H), 7.31 (d, 2H, J=8.6Hz), 7.65 (d, 2H, J=8.6Hz), 7.95 (s, 1H), 11.92 (br s, 1H).

Examples 2-8 to 2-268:

[0151] The compounds shown in Table 2 are obtained in the same manner as in Examples 2 through 2-7.

Example 3

a)



18 19

[0152] To a stirred solution of 4-hydroxy-4-phenylpiperidine (18) (1.00 g, 5.64 mmol) and Et_3N (0.94 mL, 6.77 mmol) in 10 mL of $CHCl_3$ was added ethyl oxalyl chloride (0.63 mL, 5.64 mmol) at 0 °C and stirred for 1 h. After addition of 10 mL of water, the organic layer was separated, dried over $MgSO_4$, and concentrated in vacuo to afford crude compound 19, which was used for the next reaction without further purification.

b)



19 20

[0153] Crude compound 19, 10 mL of $CHCl_3$, trifluoroacetic acid (1.52 mL, 19.7 mmol) and triethylsilane (1.52 mL, 11.3 mmol) were stirred together at 65 °C for 1.5 h. After addition of 15 mL of water, the organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt=9/1) to give compound 20 (1.38 g) as pale yellow oil.

c)

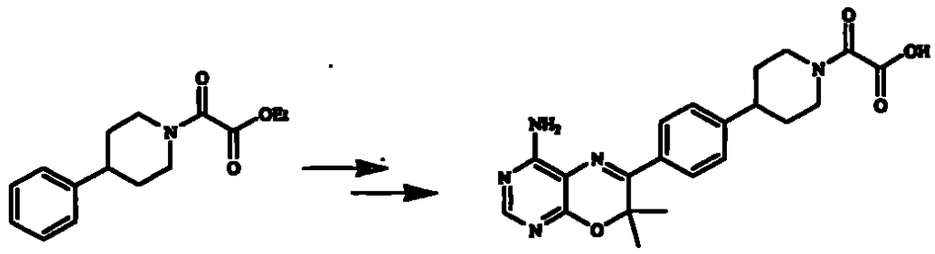


20 21

[0154] To a stirred solution of compound 20 (1.38 g, 5.32 mmol) in 8 mL of MeOH was added 10% Pd/C (200 mg). The mixture was stirred at room temperature for 5 h under an atmospheric pressure of hydrogen. The catalyst was removed by filtration, and filtrate was

concentrated in vacuo to afford crude compound 21, which was used for the next reaction without further purification.

d)



21 Ex. 3

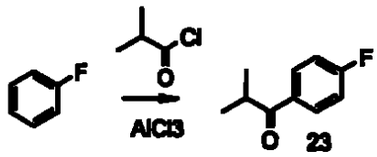
[0155] The Example 2-c) and 2-d) procedure was applied to compound 21 on a 58 mg (0.46 mmol) scale, yielding Ex. 3 (20 mg) as a colorless crystal, m.p.: 188.8-190.9 °C. IR (cm^{-1}): 1618, 1460, 1440. MS (ESI+): 410 (100). 1H NMR (DMSO-d6, 400 MHz): 1.46-1.67 (m, 2H), 1.6 (s, 6H), 1.81-1.94 (m, 2H), 2.72-2.98 (m, 2H), 3.21-3.34 (m, 1H), 3.63-3.71 (m, 1H), 4.34-4.46 (m, 1H), 6.98 (br s, 2H), 7.33 (d, 2H, J=8.4Hz), 7.67 (d, 2H, J=8.4Hz), 7.95 (s, 1H).

Example 3-2 to 3-3:

[0156] The compounds shown in Table 3 were obtained in the same manner as in Example 3.

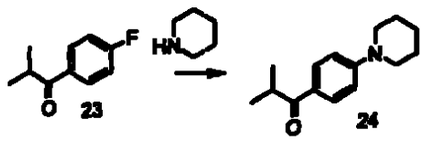
Example 4

a)



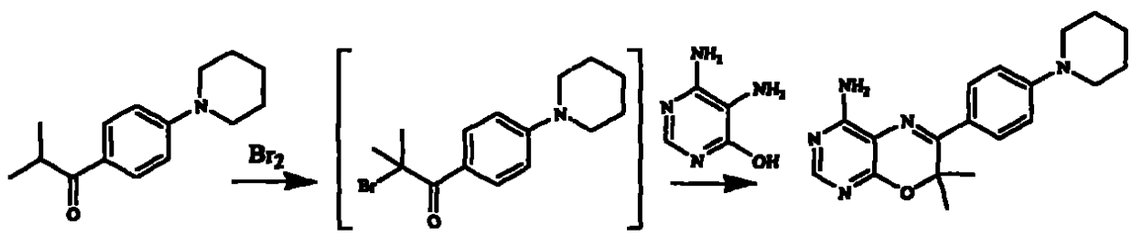
[0157] Fluorobenzene (1.78 mL, 18.96 mmol), aluminum chloride (2.53 g, 18.96 mmol) and isobutyryl chloride (1.0 mL, 9.48 mmol) were mixed under Ar and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into ice water with stirring and extracted with ether (50 mL). The organic extract was washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL) and dried over Na_2SO_4, and the solvent was removed to give compound 23 (1.47 g) as colorless oil which was pure enough to be used for the next step without further purification.

b)



[0158] To a solution of compound 23 (50 mg, 0.30 mmol) in DMSO (0.5 mL) was added piperidine (119 μL, 1.2 mmol) and the mixture was heated at 140 °C for 5 h under Ar. After cooling, the reaction mixture was diluted with ether (10 mL) and washed with 5% $KHSO_4$ (10 mL), water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed to give compound 24 (65 mg) as colorless oil, which was pure enough to be used for the next step without further purification.

c)



24 Ex. 4

[0159] To a solution of compound 24 (64 mg, 0.28 mmol) in DME (1 mL) were added 25%HBr-AcOH (100 μl, 0.31 mmol) and Br_2 (15.7 μl, 0.31 mmol) successively and the mixture was stirred at room temperature for 30 min. To the reaction mixture was added 4,5-diamino-6-hydroxypyrimidine (17.5 mg, 0.14 mmol), 1N HCl (140 μl, 0.14 mmol), EtOH (1 mL), and water (1 mL) and the mixture was refluxed overnight. After cooling, EtOH was removed under reduced pressure, and the residue was diluted with AcOEt (10 mL) and washed with 1N NaOH (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by thin-layer chromatography using as eluent $CHCl_3$-MeOH (9:1) to afford Ex. 4 (40 mg) as a pale yellow crystal, m.p.: 191-193 °C. IR (cm^{-1}): 3318, 2933, 1606, 158. MS (ESI+): 338 (100). 1H NMR (DMSO-d6, 400 MHz): 1.58-1.62 (m, 6H), 1.62 (s, 6H), 3.26 (br s, 4H), 6.79 (br s, 2H), 7.29 (d, 2H, J=9.0 Hz), 7.63 (d, 2H, J=9.0 Hz), 7.91 (s, 1H).

Example 4-2 to 4-7:

[0160] The compounds shown in Table 4 were obtained in the same manner as in Example 4.

Example 5

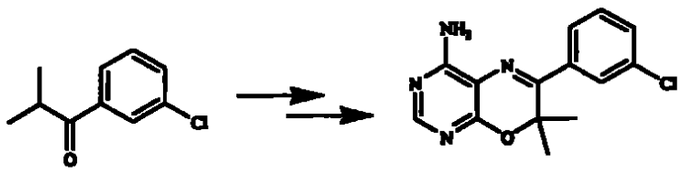
a)



27

[0161] – 3-Chloroacetophenone (0.5 mL, 3.85 mmol), powdered KOH (2.16 g, 38.5 mmol), 18-crown-6 (102 mg, 0.385 mmol), methyl iodide (1.92 mL, 30.8 mmol) and 12 mL of toluene were stirred together at room temperature for 3 days. After addition of 30 mL of water, the aqueous layer was extracted with 20 mL of AcOEt, and the extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford crude compound 27, which was used for the next reaction without further purification.

b)



27 Ex. 5

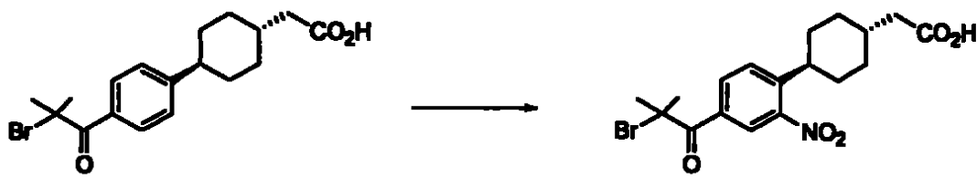
[0162] The Example 4 procedure was applied to compound 27 on a 60 mg (0.47 mmol) scale, yielding Ex. 5 (40 mg) as a colorless crystal, m.p.: 117.2-133.4 °C. IR (cm^{-1}): 1639, 1583, 1468. MS (ESI+): 289 (100). 1H NMR (DMSO-d6, 400 MHz): 1.60 (s, 6H), 7.01 (br s, 2H), 7.48 (t, 1H, J=5.9Hz), 7.55 (ddd, 1H, J=5.9, 1.3, 0.8Hz), 7.67 (ddd, 1H, J=5.9, 1.3, 0.8Hz), 7.76 (t, 1H, J=1.3Hz), 7.97 (s, 1H).

Example 5-2 to 5-3:

[0163] The compounds shown in Table 5 were obtained in the same manner as in Example 5.

Example 6

a)



22 28

[0164] To a stirred solution of compound 22 (20.0 g, 54.5 mmol) in 160 mL of $CHCl_3$ was added dropwise 96% sulfuric acid (12.1 mL, 218 mmol) and 60% nitric acid (4.56 mL, 59.9 mmol) at 0 °C and stirred at same temperature for 30 min. The reaction mixture was then poured into crashed ice (150 g). The organic layer was washed with water (50 mL) and brine (50 mL), dried over Mg2SO4, and concentrated *in vacuo*. The residue was purified by crystallization from AcOEt/Heptane (1/2,120 mL), to give compound 28 (18.4 g) as a pale yellow crystal.

b)



28 29

[0165] To a stirred suspension of Zn (15.9 g, 218 mmol) in 150 mL of acetic acid, compound 28 (15.0 g, 36.4 mmol) was added portionwise at 0 °C and stirred at room temperature for 1 hr, then stirred at 60 °C for another 30 min. The mixture was cooled to ambient temperature, filtered, and the filtrate was concentrated in vacuo. To the residue was added AcOEt (150 mL), washed with water (50 mL) and brine (50 mL), dried over Mg2SO4, and concentrated in vacuo. The residue was purified by crystallization from EtOH/H2O (3/1, 50 mL), to give compound 29 (9.36 g) as a white crystal.

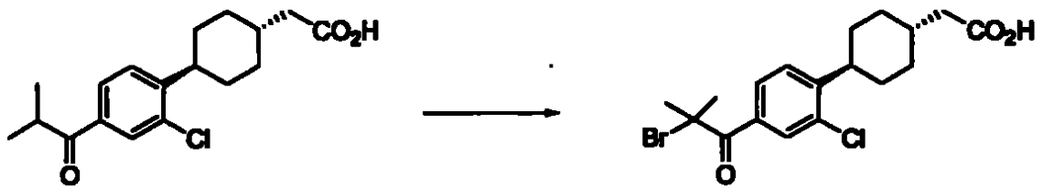
c)



29 30

[0166] To a stirred suspension of cupper chloride(II) (6.30 g, 44.5 mmol) in 135 mL of acetone was added tert-butyl nitrite (5.88 mL, 44.5 mmol) at 0 °C, then added portionwise compound 29 (9.00 g, 29.7 mmol) and stirred at same temperature for 2 h. Then the mixture was stirred at room temperature for 1 h. After addition of 2N HCl, the mixture was extracted with AcOEt (100 mL). The extract was successively washed with 1N HCl (50 mL), water (50 mL), and brine (50 mL), dried over Mg2SO4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (CHCl3/AcOEt=10/1~4/1) to give compound 30 (7.40 g) as a pale yellow crystal.

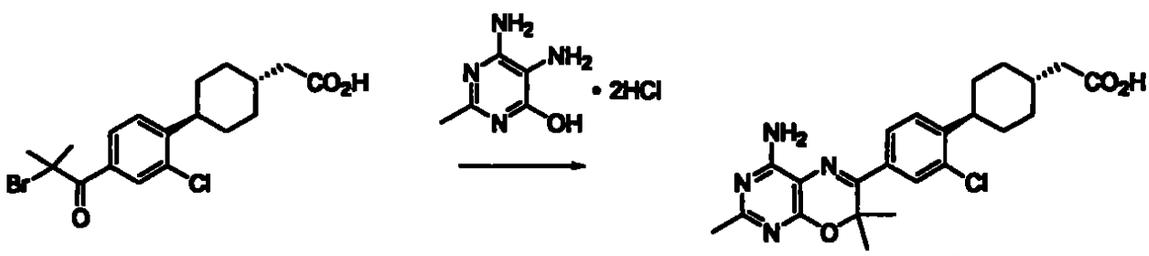
d)



30 31

[0167] To a stirred solution of compound 30 (100 mg, 0.31 mmol) in 1 mL of DME was added 25% HBr-AcOH solution (89 mL, 0.372 mmol) and bromine (19 mL, 0.37 mmol) at 0 °C and stirred for 7 hr at room temperature. After addition of water, the mixture was extracted with AcOEt, the organic layer was washed with water and brine, dried over Mg2SO4. Evaporation of the solvent gave crude compound 31 (112 mg) as a pale yellow solid, which was used for the next reaction without further purification.

e)



31 Ex. 6

[0168] To a solution of compound 31 (461 mg, 1.07 mmol) in EtOH (4 mL) was added 4,5-diamino-6-hydroxy-2-methylpyrimidine dihydrochloride (457 mg, 2.14 mmol) and water (1.3 mL), and refluxed for 12h. After cooling, to the reaction mixture was added 4N NaOH (2.5 mL, 10.0 mmol) and refluxed for 1 hr. After cooling, the reaction mixture was adjusted to pH 4 with 4N HCl and stirred for 1hr. The deposited solid was collected by filtration, washed with water, and dried in vacuo to give Ex. 6 (354 mg) as an orange solid.

f)



22 31

[0169] An alternative preparation of 31: To a stirred solution of compound 22 (100 mg, 0.272 mmol) in sulfuryl chloride (0.219 mL, 2.72 mmol) was added aluminum chloride (127 mg, 0.953 mmol) and catalytic amount of S2Cl2 at 0 °C and stirred for 2h. The reaction mixture was then poured into ice water (30 g) and extracted with AcOEt (30 mL). The organic layer was washed with water (20 mL), brine (20 mL), dried over Mg2SO4. Evaporation of the solvent gave crude compound 31, which was used for the next reaction above, without further purification.

Example 6-9:

a)

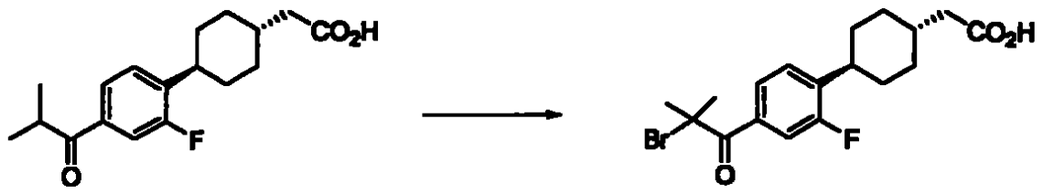


29 32

[0170] To a suspension of compound 29 (1.0 g, 3.29 mmol) in 15 mL of toluene was added nitrosonium tetrafluoroborate (462 mg, 3.95 mmol) under argon at 0 °C. After stirring for 30 min at 0 °C, the mixture was heated to 120 °C and stirred for 1 hr. After cooling, the solution was diluted with AcOEt, and the organic layer was washed with water, dried over Na_2SO_4,

and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt/$CHCl_3$/hexane =1/1/1) to give compound 32 (381 mg) as a pale yellow crystal.

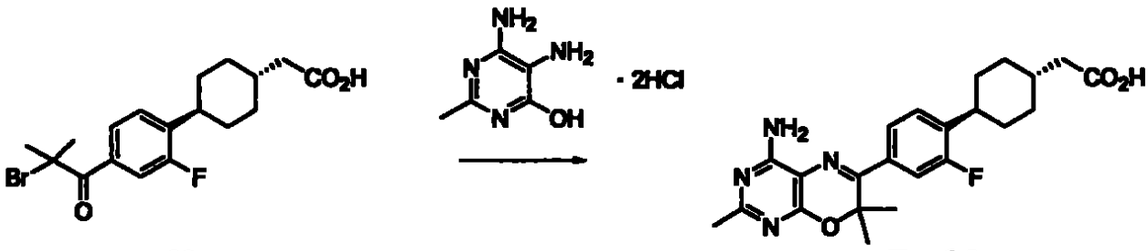
b)



32 33

[0171] To a stirred solution of compound 32 (381 mg, 1.24 mmol) in 4 mL of DME was added 25% HBr-AcOH solution (356 mL, 1.49 mmol) and bromine (76 mL, 1.49 mmol) at 0 °C and stirred for 5 min at 0 °C and for 30 min at room temperature. After addition of water, the mixture was extracted with AcOEt, the organic layer was washed with brine, dried over Na_2SO_4. Evaporation of the solvent gave crude compound 33 (454 mg) as a pale yellow solid, which was used for the next reaction without further purification.

c)



33 Ex. 6-9

[0172] To a solution of compound 33 (454 mg, 1.18 mmol) in EtOH (6 mL) was added 4,5-diamino-6-hydroxy-2-methylpyrimidine dihydrochloride (502 mg, 2.36 mmol) and water (2 mL), and refluxed for 12h. After cooling, to the reaction mixture was added 2N NaOH (5.9 mL, 11.8 mmol) and reflux for 3 hr. After cooling, the reaction mixture was adjusted to pH 4 with 2N HCl and stirred for 1hr. The deposited solid was collected by filtration, washed with water, and dried in vacuo to give Ex. 6-9 (477 mg) as a pale yellow solid.

Example 6-2 to 6-25:

[0173] The compounds shown in Table 6 were obtained in the same manner as in Examples 6 and 6-9.

Example 7

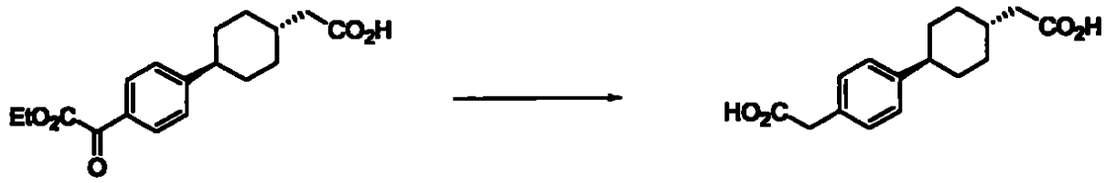
a)



34 35

[0174] To a stirred mixture of $AlCl_3$ (6.41 g, 48.1 mmol) in 30 mL of CH_2Cl_2 was added Ethyl oxalyl chloride(1.58 mL, 14.2 mmol) and compound 34 (3.0 g, 14.2 mmol) at 0 °C and stirred at 0 °C ~ room temperature for 2h. After the reaction mixture was poured into ice, 10 mL of AcOEt was added to the mixture and conc.HCl was added until suspended solution became clear. The organic layer was separated, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt=3/1~1/1) to give compound 35 (3.36 g) as a white solid.

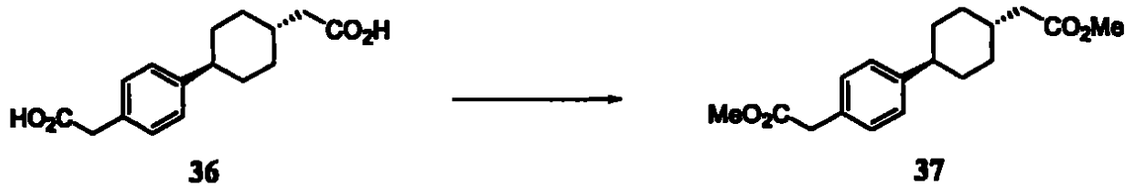
b)



35 36

[0175] The mixture of compound 35 (3.36 g, 10.5 mmol) and KOH (2.0 g, 35.8 mmol) and N2H4.H2O (1.38 mL, 28.5 mmol) in tri(ethylene glycol) (30 mL) was stirred at 175 °C for 1h. After cooling to room temperature, 2N HCl (30 mL, 60 mmol) and water (40 mL) was added and the deposited solid was collected by filtration to give compound 36 (2.58 g) as a pale yellow solid.

c)



36 37

[0176] To a stirred mixture of compound 36 (2.57 g, 9.3 mmol) in 30 mL of MeOH was added SOCl2 (1.7 mL, 23.3 mmol) at 0 °C and stirred at room temperature for 4h. The reaction mixture was concentrated in vacuo, then the residue was purified by silica gel

column chromatography (hexane/AcOEt=5/1~3/1) to give compound 37 (2.13 g) as a white solid.

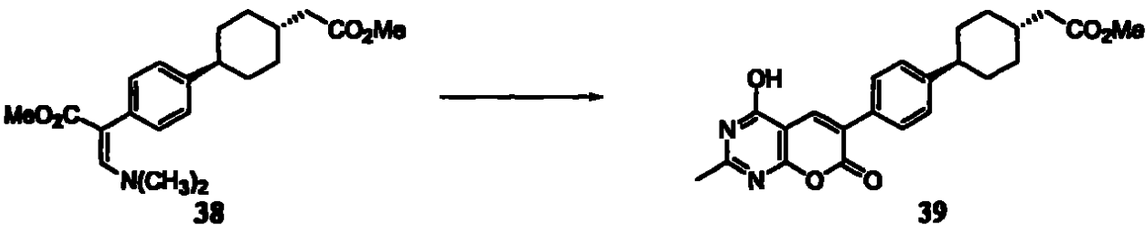
d)



37 38

[0177] The mixture of compound 37 (2.13 g, 7.0 mmol) and N,N-dimethylformamide diethyl acetal (6.8 mL, 39.7 mmol) was stirred at 130 °C for 3 days. Then toluene (20 mL) was added and the reaction mixture was concentrated in vacuo to give crude compound 38, which was then used for the next reaction without further purification.

e)



38 39

[0178] The mixture of compound 38 (crude, 7.0 mmol) and 4,6-Dihydroxy-2-methylpyrimidine (883 mg, 7.0 mmol) in AcOH (20 mL) was stirred at 110 °C for 4h. After the reaction mixture was concentrated in vacuo, EtOH (10 mL) and water (8 mL) was added and the deposited solid was collected by filtration to give compound 39 (1.12 g) as a brown solid.

f)



39 40

[0179] The mixture of compound 39 (200 mg, 0.49 mmol) and $POCl_3$ (1 mL) was stirred at 90 °C for 3h. Then the reaction mixture was poured into ice and the product was extracted with AcOEt (3mL), and the organic layer was successively washed with water (2 mL) and brine (2 mL). The organic layer was dried over $MgSO_4$, and concentrated in vacuo. The

residue was purified by silica gel column chromatography (hexane/AcOEt=2/1) to give compound 40 (174 mg) as an orange solid.

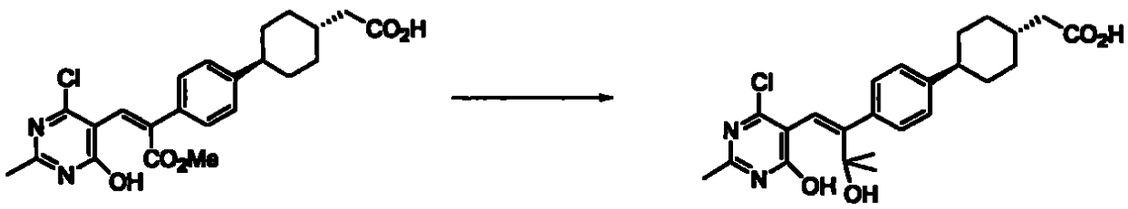
g)



40 41

[0180] The mixture of compound 40 (124 mg, 0.30 mmol) and 4N NaOH (0.41 mL, 1.65 mmol) in MeOH (5 mL) was stirred at room temperature for 19h and then stirred at 60 °C for 2.5h. After cooling to room temperature, 2N HCl (2 mL, 4 mmol) and water (10 mL) was added and the deposited solid was collected by filtration to give compound 41 (100 mg) as a pale yellow solid.

h)



41 42

[0181] To a stirred solution of 0.93M MeMgBr in THF (1.2mL, 1.12 mmol) was added the suspended solution of compound 41 (100 mg, 0.23 mmol) in THF (1.5 mL), and stirred at room temperature for 3h. After addition of water (1 mL) and 2N HCl (2 mL), the product was extracted with AcOEt (3 mL), and the organic layer was successively washed with brine (2 mL). The organic layer was dried over $MgSO_4$, and concentrated in vacuo to give crude compound 42, which was then used for the next reaction without further purification.

i)



42 43

[0182] The mixture of compound 42 (crude, 0.23 mmol) and AcOH (2 mL) was stirred at 100 °C for 40min. After cooling to room temperature, water (3 mL) was added to the reaction mixture and the product was extracted with AcOEt (3 mL), then the organic layer was successively washed with water (2 mL) and brine (2 mL). The organic layer was dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=40/1~20/1) to give compound 43 (54 mg) as a orange solid.

j)



43 44

[0183] To a stirred suspension of compound 43 (52 mg, 0.12 mmol) and K2CO3 (50 mg, 0.37 mmol) in DMF (1.5 mL) was added MeI (0.023 mL, 0.37 mmol), and the mixture was stirred at room temperature for 3h. After addition of water (3 mL), the product was extracted with AcOEt (3 mL), and the organic layer was successively washed with water (2 mL) and brine (2 mL). The organic layer was dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (Hexane/AcOEt=4/1) to give compound 44 (46 mg) as a white solid.

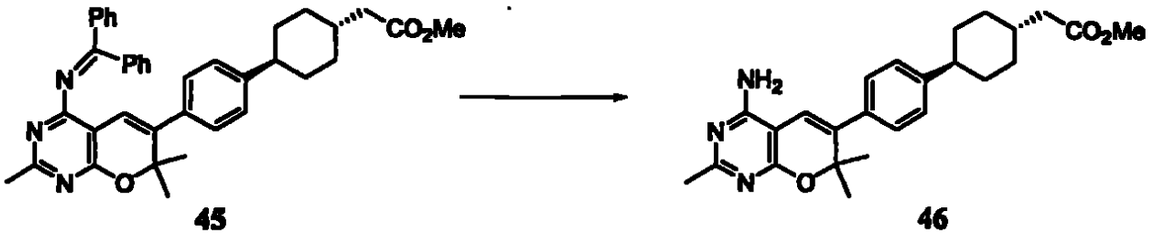
k)



44 45

[0184] To a stirred solution of compound 44 (134 mg, 0.30 mmol) in toluene (4 mL) was added Benzophenone imine (0.255 mL, 1.52 mmol) and Pd(OAc)2 (14 mg, 0.061 mmol) and (S)-(-)-BINAP (57 mg, 0.091 mmol) and CsCO3 (198 mg, 0.61 mmol), and the mixture was stirred at 110 °C for 23h. After addition of water (3 mL), the product was extracted with AcOEt (3 mL), and the organic layer was successively washed with brine (2 mL). The organic layer was dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (Hexane/AcOEt=4/1~2/1) to give compound 45 (88 mg) as a yellow solid.

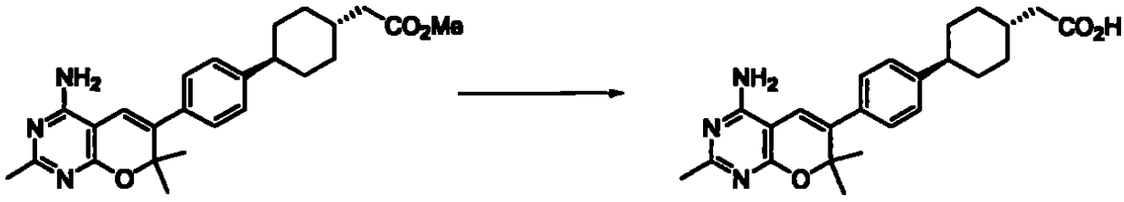
l)



45 46

[0185] To a stirred solution of compound 45 (85 mg, 0.145 mmol) in THF (2 mL) was added conc.HCl (0.050 mL), and the mixture was stirred at room temperature for 1h. After addition of 4N NaOH (0.14 mL), the product was extracted with AcOEt (5 mL), and the organic layer was successively washed with water (4 mL) and brine (4 mL). The organic layer was concentrated in vacuo, thus obtained residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=50/1) to give compound 46 (57 mg) as a yellow solid.

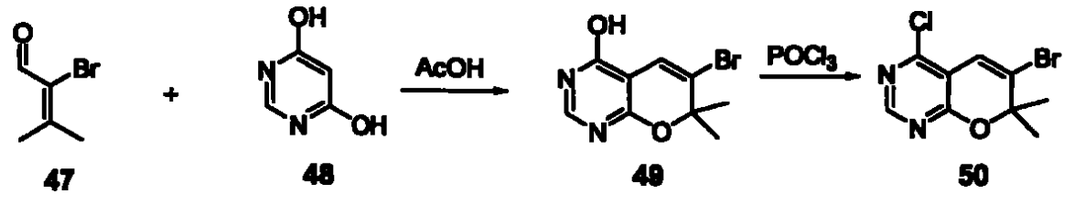
m)



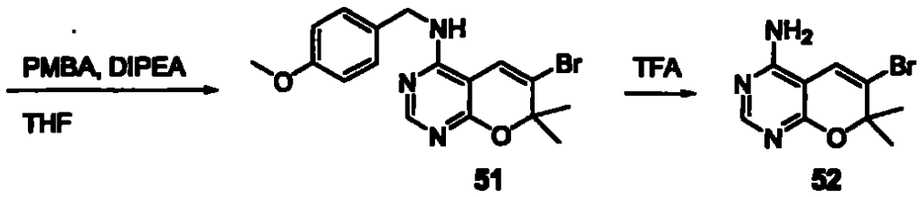
46 Ex. 7

[0186] To a stirred mixture of compound 46 (55 mg, 0.13 mmol) in mixed solvent (2 mL of THF and 3 mL of MeOH) was added 1N NaOH (0.43 mL, 0.43 mmol), and the mixture was stirred at 80 °C for 4h. After the reaction mixture was concentrated in vacuo, 2N HCl (0.25 mL, 0.5 mmol) and EtOH (1 mL) was added to the mixture and the deposited solid was collected by filtration to give Ex. 7 (38 mg) as a pale yellow solid.

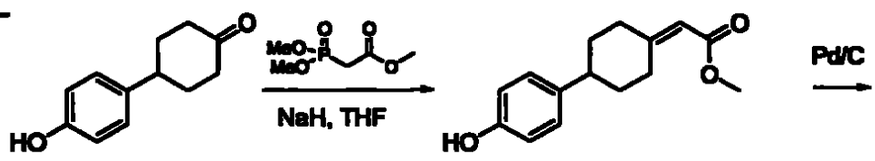
Example 7-4:



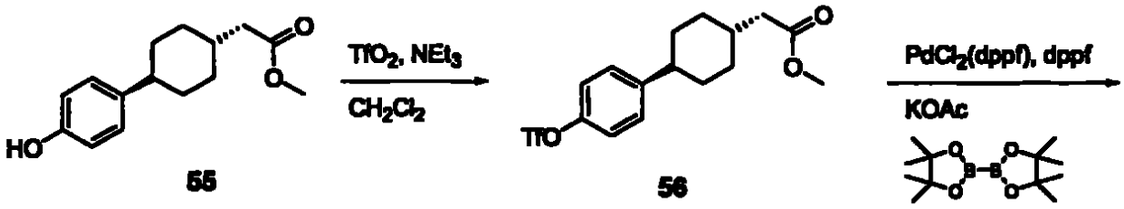
47 48 49 50



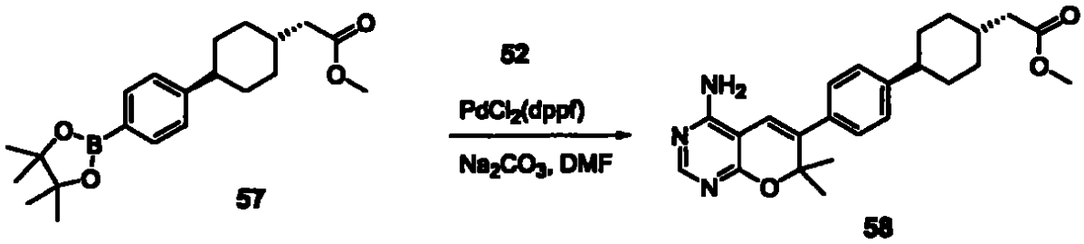
51 52



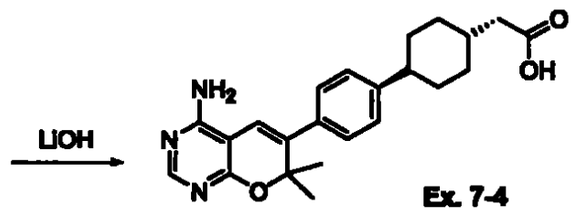
53 54



55 56



57 58



Ex. 7-4

42

[0187] **Compound 49.** A mixture of 47 (10.0 g, 89.2 mmol) and 48 (14.5 g, 89.2 mmol) in AcOH (100 mL) was heated at 100 °C for 24 h. The solvent was removed *in vacuo* and the resulting brown residue was purified by flash chromatography (silica gel 4% MeOH/CH_2Cl_2) to provide 49 as a yellow solid (12.04 g). ^{1}H NMR (DMSO-d_6) δ 8.02 (s, 1H), 6.71 (s, 1H), 1.53 (s, 6H). Mass Spectrum (ESI+) m/e = 257 and 259 (M+1).

[0188] **Compound 50.** A solution of 49 (2.13 g, 8.29 mmol) in $POCl_3$ (10 mL) was heated at 100 °C for 1 h, cooled to r.t. and poured over ice. The resulting solution was extracted with EtOAc (3 × 75 mL). The organic layers were pooled, washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide 50 as a yellow oil (2.28 g). ^{1}H NMR (DMSO-d_6) δ 8.49 (s, 1H), 7.00 (s, 1H), 1.64 (s, 6H). Mass Spectrum (ESI+) m/e = 275, 277, and 279 (M+1).

[0189] **Compound 51.** Diisopropylethylamine (1.9 mL, 10.9 mmol) was added to a solution of 50 (2.0 g, 7.26 mmol) and 4-methoxybenzylamine (2.83 mL, 21.8 mmol) in THF (20 mL). The reaction mixture was heated at reflux for 16 h, cooled to r.t., diluted with water (20 mL) and extracted with EtOAc (3 × 75 mL). The organic layers were pooled, washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a yellow solid. Purification by flash chromatography (silica gel, 50% EtOAc/hexane) provided 51 as an off-white solid (2.14 g). ^{1}H NMR (DMSO-d_6) δ 8.05 (s, 1H), 7.79 (m, 1H), 7.21 (d, J = 8.7 Hz, 2H), 7.08 (s, 1H), 6.87 (d, J = 8.7 Hz, 2H), 4.50 (d, J = 5.7 Hz, 2H), 3.71 (s, 3H), 1.50 (s, 6H). Mass Spectrum (ESI+) m/e = 376, and 378 (M+1).

[0190] **Compound 52.** A solution of 51 (620 mg, 1.65 mmol) in TFA (20 mL) was heated at 50 °C for 7 h. The solvent was removed *in vacuo* and the resulting oil was dissolved in EtOAc (30 mL), washed with saturated aqueous $NaHCO_3$ (2 × 50 mL), brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a yellow solid. The solid was sonicated in Et_2O (5 mL) and collected by vacuum filtration to provide 52 as an off-white solid (388 mg). ^{1}H NMR (DMSO-d_6) δ 7.97 (s, 1H), 7.10 (s, 1H), 7.00 (s, 2H), 1.52 (s, 6H). Mass Spectrum (ESI+) m/e = 256 and 258 (M+1).

[0191] **Compound 54.** A 60% suspension in mineral oil of NaH (211 mg, 5.23 mmol) was added to a solution of 53 (1.0 g, 5.26 mmol) in anhydrous THF (25 mL) at 0 °C under a nitrogen atmosphere. In a separate flask trimethyl phosphonoacetate (1.02 mL, 6.31 mmol) was added to a suspension of NaH (315 mg, 7.88 mmol) in anhydrous THF (25 mL) at 0 °C under a nitrogen atmosphere. After 15 min., the two mixtures were warmed to r.t. and stirred

for 30 min. The solution containing the ketone was added to the phosphonate solution *via* cannula. The reaction mixture was stirred at r.t. for 5 h, quenched with water (50 mL) and extracted with EtOAc (3 × 50 mL). The organic layers were pooled, washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide **54** as a white solid (1.25 g). ^1H NMR (DMSO-d_6) δ 9.12 (s, 1H), 7.01 (d, J = 8.4 Hz, 2H), 6.66 (d, J = 8.4 Hz, 2H), 5.70 (s, 1H), 3.82 (m, 1H), 3.62 (s, 3H), 2.70 (m, 1H), 2.33 (m, 2H), 2.01 (m, 1H), 1.92 (m, 2H), 1.47 (m, 2H). Mass Spectrum (ESI+) m/e = 247 (M+1).

[0192] **Compound 55.** A mixture of **54** (5.18 g, 21.0 mmol) and 10% Pd/C (500 mg) in EtOAc (150 mL) was stirred at r.t. under a hydrogen atmosphere for 20 h. The reaction mixture was filtered through celite and concentrated *in vacuo* to provide a yellow solid. Recrystallization from EtOAc (6 mL) provided **55** as colorless prisms with a 20:1 *trans/cis* ratio (2.96 g). ^1H NMR (DMSO-d_6) δ 9.08 (s, 1H), 6.99 (d, J = 8.5 Hz, 2H), 6.65 (d, J = 8.5 Hz, 2H), 3.60 (s, 3H), 2.33 (dt, J = 3.0 and 12.1 Hz, 1H), 2.23 (d, J = 6.9 Hz, 2H), 1.75 (m, 5H), 1.38 (m, 2H), 1.11 (m, 2H). Mass Spectrum (ESI+) m/e = 249 (M+1).

[0193] **Compound 56.** Triethylamine (421 μL, 3.02 mmol) was added dropwise to a solution of **55** (500 mg, 2.02 mmol) and trifluoromethanesulfonic anhydride (424 μL, 2.52 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was warmed to r.t. and stirred for 4.5 h, poured into water (30 mL) and the layers were separated. The organic layers were pooled, washed with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide **56** as an off-white solid (765 mg). ^1H NMR (DMSO-d_6) δ 7.42 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 3.60 (s, 3H), 2.57 (m, 1H), 2.25 (d, J = 6.6 Hz, 2H), 1.79 (m, 5H), 1.47 (m, 2H), 1.14 (m, 2H). Mass Spectrum (ESI+) m/e = 381 (M+1).

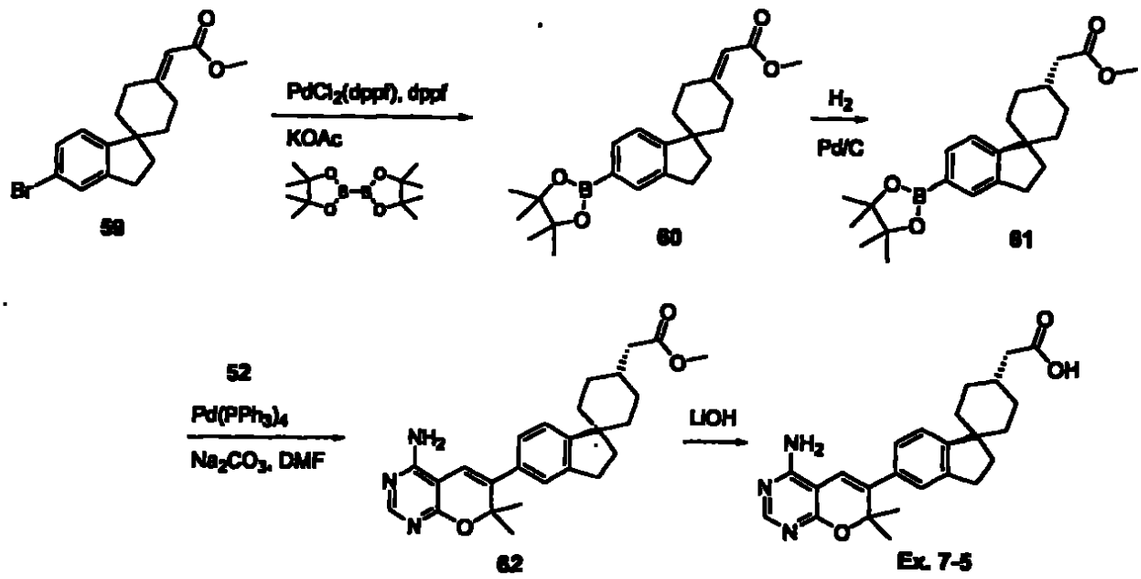
[0194] **Compound 57.** A 50 mL round-bottomed flask was charged with **56** (1.35 g, 3.55 mmol), KOAc (1.05 g, 10.6 mmol), bis(pinacolato)diboron (991 mg, 3.90 mmol), $PdCl_2$(dppf) (87 mg, 0.107 mmol), and dppf (59 mg, 0.107 mmol). The flask was consecutively filled with nitrogen and evacuated three times. Anhydrous dioxane (25 mL) was added and the reaction mixture was heated at 80 °C for 17 h. The reaction mixture was cooled to r.t., diluted with EtOAc (50 mL), washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a brown oil. Purification by flash chromatography (silica gel, 15% EtOAc/hexane) provided **57** as a white solid (914 mg). ^1H NMR (DMSO-d_6) δ 7.59 (d, J = 7.8 Hz, 2H), 7.24 (d, J = 7.9 Hz, 2H), 3.60 (s, 3H), 2.45 (m, 1H), 2.25 (d, J = 6.8 Hz,

2H), 1.78 (m, 5H), 1.46 (m, 2H), 1.28 (s, 12H), 1.14 (m, 2H). Mass Spectrum (ESI+) m/e = 359 (M+1).

[0195] **Compound 58.** A mixture of **52** (1.12 g, 4.38 mmol), **57** (2.0 g, 6.57 mmol), $PdCl_2$(dppf) (107 mg, 0.132 mmol), and 2M aqueous Na_2CO_3 (11 mL) in DMF (30 mL) was heated at 80 °C under a nitrogen atmosphere for 24 h. The solution was diluted with water (75 mL) and the resulting precipitate was collected by vacuum filtration to provide an off-white solid. Purification by flash chromatography (silica gel, 5% MeOH/CH_2Cl_2) provided **58** as a white solid (1.09 g). ^{1}H NMR (DMSO-d_6) δ 7.95 (s, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 6.86 (s, 2H), 6.57 (s, 1H), 3.61 (s, 3H), 2.47 (m, 1H), 2.25 (d, J = 6.7 Hz, 2H), 1.79 (m, 5H), 1.51 (s, 6H), 1.44 (m, 2H), 1.16 (m, 2H). Mass Spectrum (ESI+) m/e = 408.5 (M+1).

[0196] **Ex. 7-4.** A solution of **58** (130 mg, 0.319 mmol) in MeOH (12 mL) and 10% aqueous LiOH (4 mL) was heated at 100 °C for 4 h. The MeOH was removed *in vacuo* and the resulting aqueous solution was acidified with 1N HCl to pH 4. The resulting precipitate was collected by vacuum filtration to provide **Ex. 7-4** as an off-white solid (111 mg). ^{1}H NMR (DMSO-d_6) δ 8.09 (s, 1H), 7.33 (bs, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 6.61 (s, 1H), 2.47 (m, 1H), 2.15 (d, J = 6.9 Hz, 2H), 1.82 (m, 4H), 1.74 (m, 1H), 1.55 (s, 6H), 1.51 (m, 2H), 1.13 (m, 2H). Mass Spectrum (ESI+) m/e = 394 (M+1).

Example 7-5:



[0197] **Compound 60.** A 100 mL round-bottomed flask was charged with 59 (2.54 g, 7.58 mmol), bis(pinacolato)diboron (2.41 g, 9.47 mmol), KOAc (2.23 g, 22.7 mmol), $PdCl_2$(dppf) (186 mg, 0.227 mmol), and dppf (126 mg, 0.227 mmol). The flask was consecutively filled with nitrogen and evacuated three times. Anhydrous dioxane (70 mL) was added and the reaction mixture was heated at 80 °C for 17 h. The reaction mixture was diluted with EtOAc (75 mL) and washed with water, brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a brown oil. Purification by flash chromatography (silica gel, 5% EtOAc/hexane) provided 60 as a white solid (2.02 g). ^{1}H NMR (DMSO-d_6) δ 7.52 (s, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 5.74 (s, 1H), 3.71 (m, 1H), 3.62 (s, 3H), 2.89 (t, J = 7.4 Hz, 2H), 2.41 (m, 1H), 2.32 (m, 1H), 2.13 (m, 3H), 1.66 (m, 4H), 1.28 (s, 12H). Mass Spectrum (ESI+) m/e = 383 (M+1).

[0198] **Compound 61.** A mixture of 60 (2.02 g, 5.28 mmol) and 10% Pd/C (562 mg) in MeOH (50 mL) was stirred at r.t. under a hydrogen atmosphere for 21 h. The reaction mixture was filtered through celite and concentrated *in vacuo* to provide a colorless oil. Crystallization from MeOH, followed by recrystallization from CH_2Cl_2 with MeOH diffusion provided 61 as white needles with a 20:1 *trans/cis* ratio (600 mg). ^{1}H NMR (DMSO-d_6) δ 7.70 (s, 1H), 7.68 (d, J = 7.7 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 3.71 (s, 3H), 2.90 (t, J = 7.3 Hz, 2H), 2.29 (d, J = 7.0 Hz, 2H), 1.99 (t, J = 7.4 Hz, 2H), 1.90 (m, 1H), 1.76 (m, 2H), 1.68 (m, 2H), 1.60 (m, 2H), 1.35 (s, 12H), 1.25 (m, 2H). Mass Spectrum (ESI+) m/e = 385 (M+1).

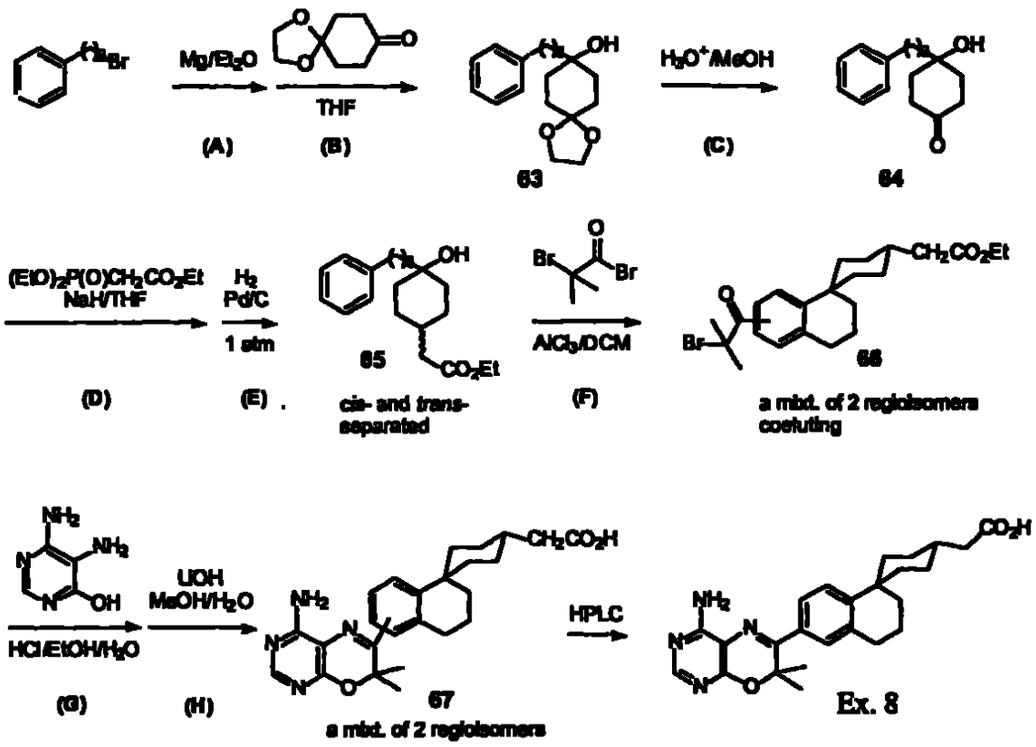
[0199] **Compound 62.** A mixture of 52 (100 mg, 0.391 mmol), 61 (150 mg, 0.391 mmol), $Pd(PPh_3)_4$ (23 mg, 0.020 mmol), and 2M aqueous Na_2CO_3 (1 mL) in DMF (10 mL) was heated at 80 °C for 3.5 h. The reaction mixture was diluted with EtOAc (75 mL), washed with water (3 × 50 mL), brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a yellow solid. Purification by flash chromatography (silica gel, 5% MeOH/CH_2Cl_2) provided 62 as a white solid (103 mg). ^{1}H NMR (DMSO-d_6) δ 7.95 (s, 1H), 7.18 (m, 3H), 6.84 (s, 2H), 6.56 (s, 1H), 3.61 (s, 3H), 2.85 (t, J = 7.3 Hz, 2H), 2.28 (d, J = 7.0 Hz, 2H), 1.95 (t, J = 7.3 Hz, 2H), 1.79 (m, 1H), 1.65 (m, 5H), 1.51 (s, 6H), 1:49 (m, 1H), 1.23 (m, 2H). Mass Spectrum (ESI+) m/e = 434 (M+1).

[0200] **Ex. 7-5.** A solution of 62 (103 mg, 0.238 mmol) in MeOH (9 mL) and 10% aqueous LiOH (3 mL) was heated at 100 °C for 2 h. The MeOH was removed *in vacuo* and the resulting aqueous layer was acidified to pH 1 with 1N HCl. The resulting precipitate was

collected by vacuum filtration to provided Ex. 7-5 as an off-white solid (73 mg). ^{1}H NMR (DMSO-d_6) δ 8.14 (s, 1H), 7.50 (bs, 2H), 7.20 (m, 3H), 6.61 (s, 1H), 2.86 (t, J = 7.2 Hz, 2H), 2.17 (d, J = 6.8 Hz, 2H), 1.96 (t, J = 7.3 Hz, 2H), 1.71 (m, 1H), 1.67 (m, 2H), 1.63 (m, 3H), 1.56 (s, 6H), 1.50 (m, 2H), 1.22 (m, 2H). Mass Spectrum (ESI+) m/e = 420 (M+1).

[0201] The compounds shown in Table 7 were obtained in the same manner as in Examples 7, 7-4 and 7-5.

Example 8



[0202] Steps (A), (B) and (C). Into a flame-dried 1L 3-necked round bottom flask equipped with a magnetic stirrer, a reflux condenser and an addition funnel was placed magnesium turnings (1.1 equiv., 8.8 g) and diethyl ether (60 mL) under a nitrogen atmosphere. A diethyl ether solution of 1-bromo-3-phenylpropane (322.4 mmol, 65.5 g) was added *via* addition funnel at such a rate that a gentle reflux was maintained throughout the addition, about 1 h 10 min. A few particles of iodine were introduced at the beginning of the addition to initiate the reaction. Upon completion of the addition of the bromide, the reaction mixture was heated at reflux for 1 h, allowed to cool to room temperature and further cooled in an ice bath. A solution of 1,4-cyclohexanedione monoethylene ketal (1 equiv., 51.91 g) in THF (100 mL) was slowly added to the ice-cooled mixture *via* addition funnel with stirring

over 1 h 30 min. The mixture was continuously stirred for 30 min. in the ice bath and overnight at ambient temperature. The reaction mixture was pre-cooled in an ice bath and mixture of ice and 4N aqueous HCl was added. The mixture was stirred until magnesium all dissolved, the layers were separated and the aqueous layer was extracted with diethyl ether (2x). The combined organics were washed with brine to neutral, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was taken onto the next step, in which it was hydrolyzed in a refluxing mixture with MeOH (400 mL) and 3 N aqueous H_2SO_4 (100 mL) for 6 h. The reaction mixture was cooled, concentrated *in vacuo*, diluted with ice water and extracted with EtOAc (2x). The combined organics were washed with brine (2x), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Column chromatography (EtOAc/hexanes, 35/65) of the residue provided the desired hydroxyketone 64 (30 g). ^{1}H NMR ($CDCl_3$) δ 1.45 (br s, 1H), 1.59-1.63 (m, 2H), 1.73-1.83 (m, 4H), 1.93-1.97 (m, 2H), 2.20-2.28 (m, 2H), 2.65-2.76 (m, 4H), 7.19-7.24 (m, 3H), 7.28-7.33 (m, 2H). Mass Spectrum (CI+) m/e = 215.1 (M + 1).

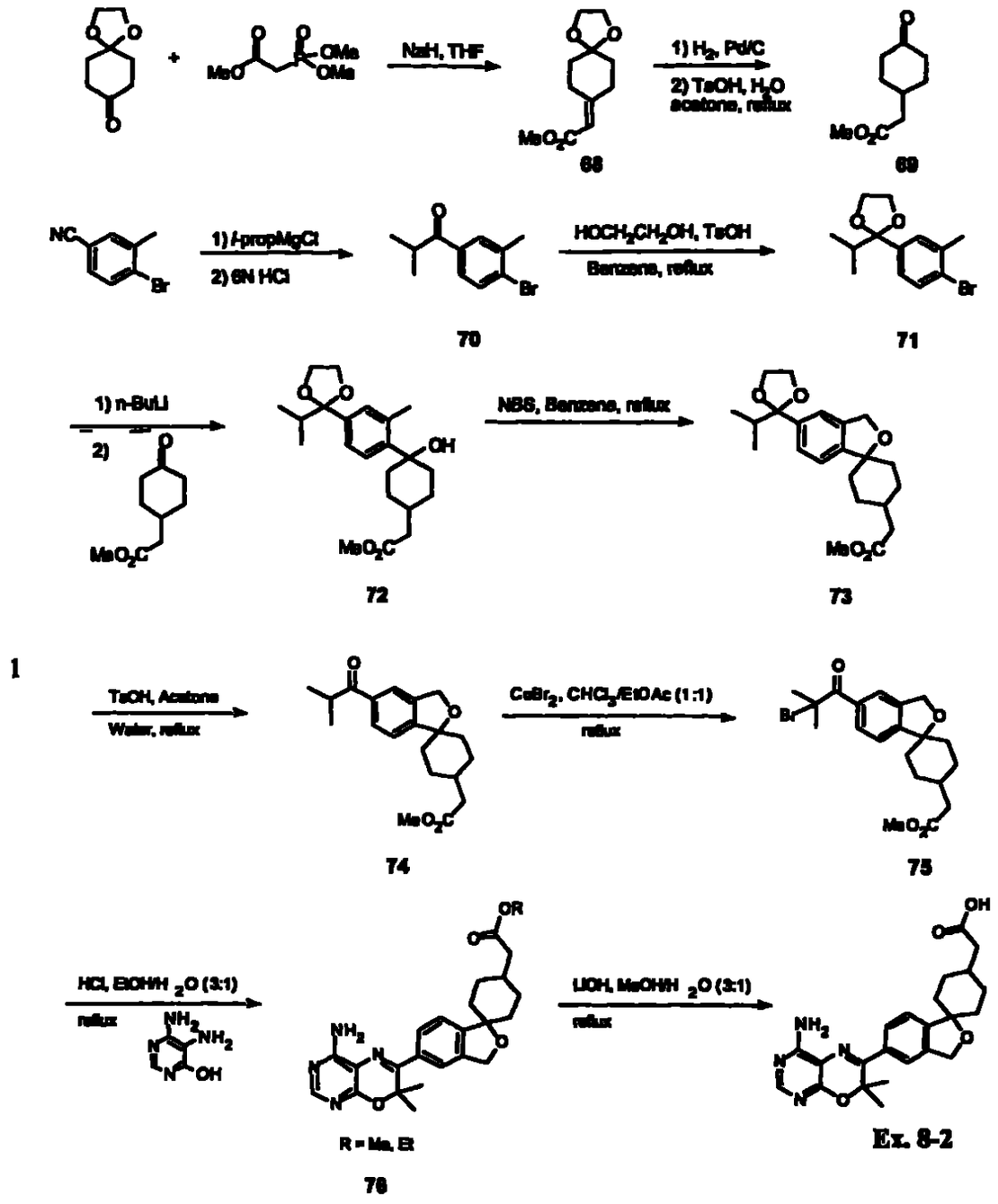
[0203] Step (D). To a flame-dried single-necked round bottom flask in an ice bath was placed NaH (a 60% dispersion in mineral oil) (1 equiv., 0.66 g) and subsequently charged with THF (20 mL) under a nitrogen atmosphere. To this was dropwise added trimethyl phosphonoacetate (1 equiv., 2.89 g/2.75 mL) *via* syringe. When hydrogen evolution appeared complete, a solution of hydroxyketone 64 (15.5 mmol, 3.33 g) in THF (40 mL) was slowly introduced *via* addition funnel. The reaction mixture was stirred at ambient temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl followed by water and extracted with EtOAc (2x). The combined organics were washed with brine (2x), dried over anhydrous sodium sulfate and concentrated *in vacuo*. Column chromatography of the residue (EtOAc/hexanes, 30/70) provided the desired hydroxyacrylate (3.5 g). ^{1}H NMR ($CDCl_3$) δ 1.16 (s, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.51-1.61 (m, 4H), 1.70-1.80 (m, 4H), 2.10-2.14 (m, 1H), 2.43-2.59 (m, 2H), 2.65 (t, J = 7.5 Hz, 2H), 3.46-3.50 (m, 1H), 4.16 (q, J = 7.1 Hz, 2H), 5.65 (s, 1H), 7.19-7.22 (m, 3H), 7.28-7.32 (m, 2H).

[0204] Step (E). The hydroxyacrylate (15.5 mmol) obtained above was hydrogenated over palladium (10% on charcoal) (10 mol%) in EtOAc (60 mL) using hydrogen gas at an atmospheric pressure over 10 h. The Pd/C was filtered off by a layer of celite and the filtrate was concentrated *in vacuo*. The product contained a mixture of two conformers (ratio 3:1) of the desired tertiary hydroxyl ester 65, which were separated by column chromatography (EtOAc/hexanes, 20/80) and characterized by the following spectral data. In practice, the

conformeric mixture was further elaborated without separation. ^{1}H NMR (major conformer, $CDCl_3$) δ 1.06 (s, 1H), 1.27 (t, J = 7.1 Hz, 3H), 1.33-1.42 (m, 4H), 1.46-1.51 (m, 2H), 1.55-1.66 (m, 4H), 1.68-1.76 (m, 3H), 2.23 (d, J = 7.0 Hz, 2H), 2.63 (t, J = 7.6 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 7.18-7.23 (m, 3H), 7.28-7.32 (m, 2H). Mass Spectrum (CI+) m/e = 287.1 (M + 1); ^{1}H NMR (minor conformer, $CDCl_3$) δ 1.07-1.15 (m, 2H), 1.22 (s, 1H), 1.27 (t, J = 7.1 Hz, 3H), 1.39-1.44 (m, 2H), 1.54-1.58 (m, 2H), 1.67-1.75 (m, 6H), 1.88 (m, 1H), 2.22 (d, J = 7.1 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 7.18-7.22 (m, 3H), 7.29-7.32 (m, 2H). Mass Spectrum (CI+) m/e = 287.1 (M + 1).

[0205] Steps (F), (G) and (H). To a flame-dried 50 mL single-necked round bottom flask in an ice-salt-bath was placed $AlCl_3$ (2.5 equiv., 1.43 g) followed by dropwise addition of 2-bromoisobutyryl bromide (2 equiv., 2.01 g/1.08 mL) under a nitrogen atmosphere. The mixture was stirred for about 5 min., and CH_2Cl_2 (8 mL) was introduced. After another 5 min, a CH_2Cl_2 (20 mL) solution of the conformeric mixture of tertiary hydroxyl ester 65 (4.3 mmol, 1.23 g) was dropwise added. The reaction mixture was continuously stirred in the ice-salt bath for 1 h. A mixture of ice and 2 N aqueous HCl was added and the mixture was stirred until all dissolved and extracted with CH_2Cl_2 (2x). The combined organics were washed with brine (3x), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue contained mainly two acylation regioisomers in a ratio of about 4 to 1, which were cyclized with 4,5-diamino-6-hydroxypyrimidine hemisulfate (0.5 equiv., 0.63 g) in the presence of 2N aqueous HCl (2.2 equiv., 4 mL) in 3:1 EtOH-H_2O (40 mL). The mixture was refluxed for about 12 h. The mixture was cooled, diluted with saturated aqueous NH_4Cl and extracted with EtOAc (2x). The combined organics were washed with saturated aqueous NH_4Cl (2x), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The product was hydrolyzed by LiOH-H_2O (5 equiv., 0.73 g) in 3:1 MeOH-H_2O (20 mL). Using the same workup used in the preceding cyclization step, a mixture of two major regioisomers (67) was obtained. The major isomer (1.2 g) was obtained by recrystallization ($EtOAc/CH_2Cl_2$/MeOH). The desired isomer (Ex. 8) (200 mg) was obtained by preparatory HPLC of the mother liquor. ^{1}H NMR ($CDCl_3$) (a single conformer, *trans*-) δ 1.35-1.43 (m, 2H), 1.69-1.88 (m, 16 H), 1.96 (m, 1H), 2.36 (d, J = 7.0 Hz, 2H), 2.83 (t, J = 6.0 Hz, 2H), 7.34 (d, J = 1.6 Hz, 1H), 7.42 (dd, J = 8.4, 1.6 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 8.16 (s, 1H). Mass Spectrum (CI+) m/e = 435.2 (M + 1).

Example 8-2:



1

[0206] **Compound 69.** Trimethyl phosphonoacetate (10.36 mL, 64.0 mmol) was added to a suspension of NaH in anhydrous THF (500 mL) at 0 °C under a nitrogen atmosphere. After 30 min. at 0 °C, a solution of 1,4-cyclohexanedione *mono*-ethylene ketal (10.0 g, 64.0 mmol) in anhydrous THF (50 mL) was added *via* cannula. The reaction mixture was warmed to ambient temperature and stirred for 12 h. The reaction was quenched with water and the THF was removed *in vacuo*. The aqueous layer was extracted with EtOAc and the organic

layers were pooled, washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to provide 68 as a colorless oil. 10% Pd/C was added to a solution of 68 in 95% EtOH (200 mL). The reaction mixture was stirred under a hydrogen atmosphere for 20 h, filtered through celite, and concentrated in vacuo to provide a colorless oil. *p*-Toluenesulfonic acid monohydrate (1.21 g, 6.40 mmol) was added to a solution of the oil in acetone (200 mL) and water (50 mL) and the reaction mixture was heated at reflux for 24 h. The acetone was removed *in vacuo* and the aqueous solution was extracted with EtOAc. The organic layers were pooled, washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide 69 as a colorless liquid (5.86 g). ^{1}H NMR ($CDCl_3$) δ 1.46 (m, 2H), 2.08 (m, 2H), 2.25-2.33 (m, 3H), 2.37 (m, 4H), 3.68 (s, 3H). Mass Spectrum (ESI+) m/e = 171.1 (M+H).

[0207] **Compound 70.** Isopropylmagnesium chloride (25.5 mL, 51.0 mmol) was added *via* syringe to a solution of 4-bromo-3-methylbenzonitrile (5.0 g, 25.5 mmol) in anhydrous Et_2O (50 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was heated at reflux for 12 h. The reaction mixture was cooled to 0 °C and quenched with 6 N HCl. After stirring at ambient temperature for 12 h, the layers were separated and the aqueous solution was extracted with EtOAc. The organic extracts were pooled, washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to provide a brown oil. Flash chromatography (silica gel, 2% EtOAC/hexanes) provided 70 as a colorless oil (3.69 g). ^{1}H NMR (DMSO-d_6) δ 1.08 (d, J = 6.8 Hz, 6H), 2.41 (s, 3H), 3.62 (m, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.92 (s, 1H). Mass Spectrum (ESI+) m/e = 241.1 and 243.1 (M+H).

[0208] **Compound 71.** *p*-Toluenesulfonic acid monohydrate (360 mg, 1.89 mmol) was added to a solution of 70 (4.57 g, 18.9 mmol) and ethylene glycol (8.45 mL, 0.152 mol) in benzene (50 mL). The reaction mixture was heated at reflux for 20 h while removing water using a Dean-Stark trap. The solution was washed with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide a colorless oil. Flash chromatography (silica gel, 2% EtOAc/hexanes) provided 71 as a colorless oil (4.86 g). ^{1}H NMR (DMSO-d_6) δ 0.79 (d, J = 6.8 Hz, 6H), 2.03 (m, 1H), 2.34 (s, 3H), 3.63 (m, 2H), 3.92 (m, 2H), 7.07 (dd, J = 2.2 and 8.2 Hz, 1H), 7.30 (d, J = 2.1 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H). Mass Spectrum (ESI+) m/e = 285.0 and 287.1 (M+H).

[0209] **Compound 72.** n-BuLi (5.4 mL, 13.5 mmol) was added to a solution of 71 (3.50 g, 12.3 mmol) in anhydrous THF (20 mL) at –78 °C. The solution was stirred at –78 °C for 30 min. and added to a solution of 69 (2.30 g, 13.5 mmol) in anhydrous THF (20 mL) at –78 °C.

The reaction mixture was warmed to ambient temperature and stirred for 12 h. The reaction was quenched with saturated aqueous NH_4Cl and the layers were separated. The aqueous layer was extracted with EtOAc and the organic extracts were pooled, washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide a yellow oil. Flash chromatography (silica gel, 15% EtOAc/hexanes) provided 72 as a colorless oil as a mixture of *cis* and *trans* isomers (2.24 g). ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 6.8 Hz, 6H), 0.88 (d, J = 6.8 Hz, 6H), 1.60-2.40 (m, 24H), 2.60 (s, 3H), 2.62 (s, 3H), 3.66 (s, 3H), 3.68 (s, 3H), 3.75 (m, 4H), 3.98 (m, 4H), 7.15-7.26 (m, 4H), 7.33 (m, 2H). Mass Spectrum (ESI+) m/e = 359.2 ([M-H_2O]+H).

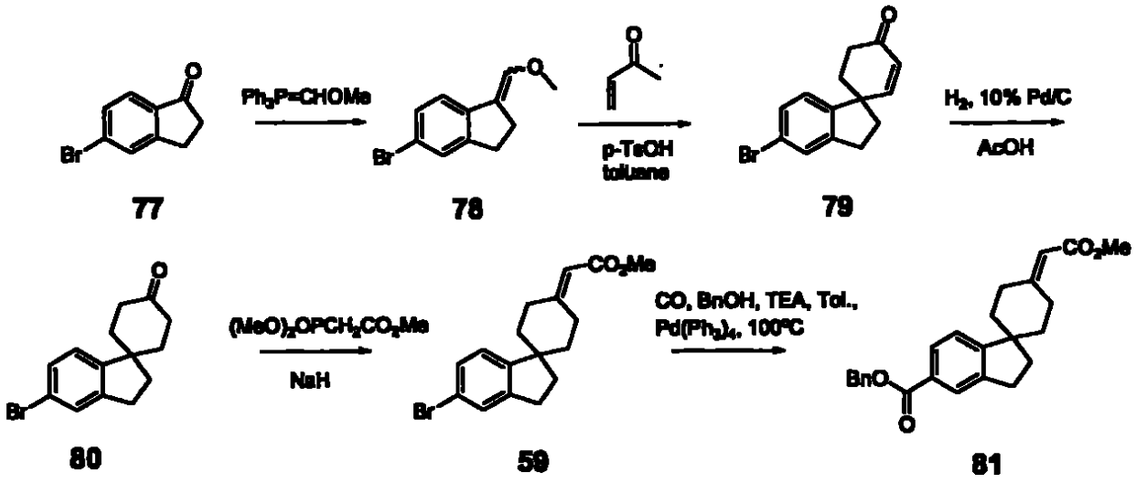
[0210] – **Compound 73.** A solution of NBS (260 mg, 1.46 mmol) and 72 (500 mg, 1.33 mmol) in benzene (100 mL) was heated at reflux for 24 h. The reaction mixture was cooled to ambient temperature, washed with water, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide a brown oil. Flash chromatography (silica gel, 10% EtOAc/hexanes) provided 73 as a yellow oil as a mixture of *cis* and *trans* isomers (187 mg). ^1H NMR (DMSO-d_6) δ 0.88 (d, J = 6.8 Hz, 6H), 0.89 (d, J = 6.8 Hz, 6H), 1.54-2.10 (m, 20H) 2.28 (d, J = 7.0 Hz, 2H), 2.43 (d, J = 7.3 Hz, 2H), 3.68 (s, 3H), 3.70 (s, 3H), 3.76 (m, 4H), 3.97 (m, 4H), 5.02 (s, 2H), 5.03 (s, 2H), 7.00 (d, J = 7.8 Hz, 1H), 7.22 (m, 3H), 7.28 (m, 2H). Mass Spectrum (ESI+) m/e = 375.1 (M+H).

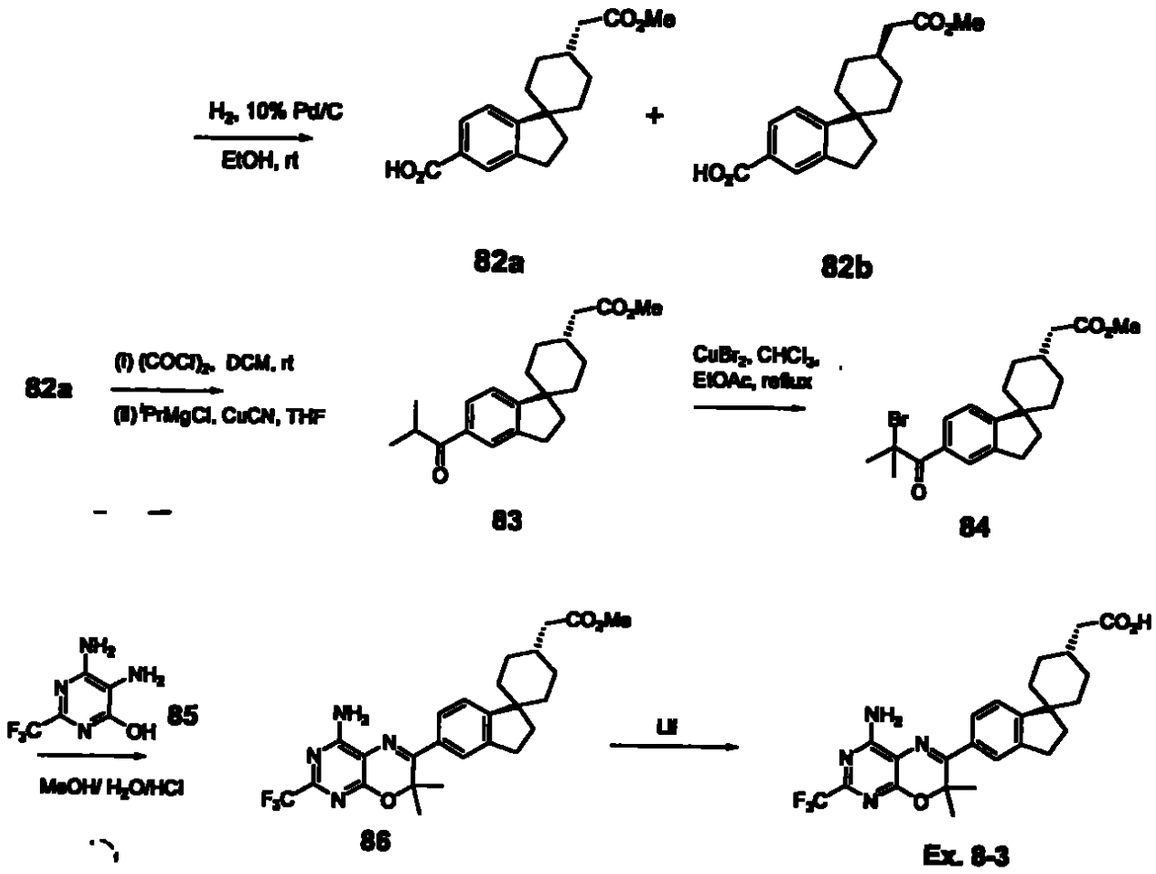
[0211] **Compound 74.** A solution of 73 (450 mg, 1.20 mmol) and *p*-toluenesulfonic acid monohydrate (23.0 mg, 0.120 mmol) in acetone (25 mL) and water (5 mL) was heated at reflux for 24 h. The acetone was removed *in vacuo* and the aqueous solution was extracted with EtOAc. The organic layers were pooled, washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide a yellow oil as a mixture of *cis* and *trans* isomers (366 mg). ^1H NMR (DMSO-d_6) δ 1.09 (d, J = 6.8 Hz, 6H), 1.09 (d, J = 6.8 Hz, 6H), 1.40-1.83 (m, 18H) 2.25 (d, J = 7.0 Hz, 2H), 2.53 (d, J = 7.4 Hz, 2H), 3.59 (s, 3H), 3.60 (s, 3H), 3.63 (m, 2H), 4.98 (s, 4H), 7.38 (d, J = 7.9 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.87 (m, 4H). Mass Spectrum (ESI+) m/e = 331.2 (M+H).

[0212] A mixture of 74 (400 mg, 1.21 mmol) and $CuBr_2$ (811 mg, 3.63 mmol) in $CHCl_3$ (25 mL) and EtOAc (25 mL) was heated at reflux for 5 h. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc and water. The layers were separated and the aqueous solution was extracted with EtOAc. The organic layers were pooled, washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide 75 as a yellow oil. 4,5-

Diamino-6-hydroxypyrimidine hemisulfate (170 mg, 0.486 mmol) and 2 N HCl (535 μL, 1.07 mmol) were added to a solution of 75 (398 mg, 0.972 mmol) in EtOH (18 mL) and water (6 mL). The reaction mixture was heated at reflux for 23 h and quenched with saturated aqueous NH_4Cl. The solution was extracted with EtOAc and the organic layers were pooled, washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide 76 as an orange foam (360 mg). Lithium hydroxide monohydrate (173 mg, 4.12 mmol) was added to a solution of 76 (360 mg, 0.825 mmol) in MeOH (18 mL) and water (6 mL). The reaction mixture was heated at reflux for 18 h and quenched with NH_4Cl. The solution was acidified with HCl and extracted with EtOAc. The organic layers were pooled, washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide Ex. 8-2 as a yellow solid (146 mg), as a mixture of *cis* and *trans* isomers which were separated by reverse phase HPLC. ^1H NMR (major isomer, DMSO-d_6) δ 1.50 (m, 5H), 1.61 (s, 6H), 1.82 (m, 4H), 2.40 (d, J = 7.3 Hz, 2H), 4.97 (s, 2H), 7.53 (d, J = 7.9 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.62 (s, 1H), 7.99 (s, 1 H). Mass Spectrum (CI+) m/e = 423.2 (M + 1). ^1H NMR (minor isomer, DMSO-d_6) δ 1.40 (m, 2H), 1.60 (s, 6H), 1.64 (m, 4H), 1.75 (m, 3H), 2.15 (d, J = 6.9 Hz, 2H), 4.97 (s, 2H), 7.30 (d, J = 8.5 Hz, 1H), 7.61 (m, 2H), 7.98 (s, 1H). Mass Spectrum (CI+) m/e = 423.2 (M+1).

Example 8-3:





[0213] **Compound 78.** To a stirred suspension of potassium *tert*-butoxide (16.2 g, 142 mmol) in 1,4-dioxane (300 mL) was added (methoxymethyl)triphenyl-phosphonium chloride (48.5 g, 142 mmol) at r.t. under N_2. After stirring for 2 h, 5-bromoindanone (77, 13 g, 61.6 mmol) in dioxane (170 mL) was added to the solution at r.t. under N_2. The mixture was stirred for 2 h at r.t., poured into water (500 mL) and extracted with EtOAc (500 mL). The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. To the residue was added hexane:EtOAc (2:1 (500mL)). The mixture was stirred at r.t., filtered and the precipitate washed with 2x hexane:EtOAc (2:1 (500mL)). The filtrate was concentrated *in vacuo* and the residue distilled (700mm torr at 145-150 °C) to give compound 78 as a light yellow solid of the *cis* and *trans* mixture (14.5 g). ^{1}H NMR ($CDCl_3$) δ 2.70-2.80 (m, 2H, major and minor isomers), 2.94-3.00 (m, 2H, major and minor isomers), 3.75 (s, 3H, major and minor isomers), 6.20 (t, J = 1.8 Hz, 1H, minor isomer only), 6.65 (t, J = 2.6 Hz, 1H, major isomer only), 7.12 (d, J = 8.2 Hz, 1H, major isomer only), 7.22-7.34 (m, 2H, major and minor isomers), 7.68 (d, J = 8.2 Hz, 1H, minor isomer only).

[0214] **Compound 79.** To a stirred solution of 78 (14.5 g, 60.8 mmol) in toluene (60 mL) was added methylvinyl ketone (6.0 mL, 68 mmol) and *p*-toluenesulfonic acid monohydrate

(1.2 g, 6.3 mmol) at r.t.. The mixture was heated at 100 °C for 18 h under N_2, allowed to cool to r.t. and poured into sat. aqueous $NaHCO_3$ solution (200 mL). The organic layer was separated and washed with brine. The aqueous layer was extracted with EtOAc and the organic layer was separated and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was recrystallized from EtOH:H_2O (2:1 (168mL)), filtered and dried *in vacuo* at 60 °C to give 79 as a pale yellow solid (9.90g). ^1H NMR ($CDCl_3$) δ 2.09-2.24 (m, 3H), 2.29-2.32 (m, 1H), 2.54 (dd, J = 7.2, 6.3 Hz, 2H), 2.99-3.12 (m, 2H), 6.10 (d, J = 10.1 Hz, 1H), 6.76 (d, J = 10.1 Hz, 1H), 6.99 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.44 (s, 1H).

[0215] – **Compound 80.** To a stirred solution of 79 (153.4 g, 0.55 M) in acetic acid (3.7 L) was added 10% Pd/C (30 g). The mixture was stirred under an atmosphere of hydrogen for 4 h and filtered through silica gel (washing with acetic acid followed by DCM). The filtrate was concentrated *in vacuo* to afford 80 as a white solid (150.51 g). ^1H NMR ($CDCl_3$) δ 1.90-1.97 (m, 2H), 2.02-2.12 (m, 2H), 2.26 (t, J = 7.3 Hz, 2H), 2.43-2.61 (m, 4H), 3.01 (t, J = 7.3 Hz, 2H), 7.04 (d, J = 8.1 Hz, 1H), 7.32-7.35 (m,1H), 7.40 (s, 1H).

[0216] **Compound 59.** To a stirred solution of trimethyl phosphonoacetate (116.45 g, 640 mmol.) in anhydrous THF (2.2 L) under an atmosphere of N_2 at 0 °C was added portionwise over 7 min. sodium hydride (25.6 g of a 60% dispersion in mineral oil, 640 mmol.). The mixture was stirred at 0 °C for 30 min. and allowed to warm to r.t. over 30 min. A solution of 80 (149 g, 533 mmol.) in anhydrous THF (375 mL) was added over 10 min. The mixture was stirred at r.t. for 90 min. and saturated aqueous NH_4Cl (500 mL) was added. The mixture was stirred for 5 min. and concentrated *in vacuo* to remove the THF. The aqueous phase was washed with diethyl ether (1 L and 500 mL). The combined organic fractions were washed with brine solution, dried ($MgSO_4$) and concentrated *in vacuo*. Trituration of the resulting oily residue afforded a white solid which was collected by filtration and washed with hexane to give 59 (62.0 g). The mother liquor was concentrated *in vacuo* and the residue recrystallized from EtOAc/hexane at 0 °C to afford additional 59 (38.3 g). A further three iterations of the above recrystallization method afforded additional 59 (40.5 g). ^1H NMR ($CDCl_3$) δ 1.68-1.78 (m, 4H), 2.11-2.21 (m, 3H), 2.31-2.46 (m, 2H), 2.95 (t, J = 7.4 Hz, 2H), 3.73 (s, 3H), 3.82-3.87 (m, 2H), 5.73 (s, 1H), 6.99 (d, J = 8.0 Hz, 2H), 7.29-7.32 (m,1H), 7.37 (s, 1H).

[0217] **Compound 82a.** To a 5 L 3-necked round bottom flask containing **59** (140 g, 418 mmol) was added Et_3N (280 mL, 2.03 mol), benzyl alcohol (420 mL, 4.06 mmol) and toluene (1.4 L). The resulted solution was purged with CO for 5 min. before addition of $Pd(PPh_3)_4$ (9.34 g, 8 mmol). The reaction was heated to 90 °C for 8 h with purging of CO. The mixture was stirred in an ice bath for 30 min. and filtered, and the precipitate washed with EtOAc. The filtrate was washed with water, brine and dried over sodium sulfate. The solvents and the excess benzyl alcohol were removed *in vacuo*. The residue was dissolved in DCM (50 mL) and hexane (50 mL) and filtered through a funnel filled with silica gel (500 g). The pad was washed with hexane/EtOAc (gradient elution: 9/1 to 1/1). Concentration *in vacuo* afforded **81** as yellow oil (160 g). Compound **81** was dissolved in EtOH (12 L) and Pd on carbon (10%, 20 g) was added. The mixture was stirred under an atmosphere of hydrogen for 2 days, filtered through a pad of celite and concentrated *in vacuo* to give a white solid (120 g). To the crude product was added EtOAc (200 mL) and the mixture was heated to reflux for 1 min. and filtered. The filtrate was reheated to reflux and hexane was added slowly. The resulting mixture was cooled slowly to r.t. to afford a white crystalline solid which was collected by filtration (44 g of the *trans* isomer **82a**). The mother liquor was concentrated and recrystallization from EtOAc: hexane afforded an additional 16 g of **82a**. ^1H NMR ($CDCl_3$) δ 1.23-1.27 (m, 2H), 1.59-1.90 (m, 7H), 2.03 (t, J = 7.4 Hz, 2H), 2.28 (d, J = 7.0 Hz, 2H), 2.93 (t, J = 7.4 Hz, 2H), 3.70 (s, 3H), 7.21 (d, J = 7.9 Hz, 1H), 7.93 (s, 1H), 7.95 (d, J = 7.9 Hz, 1H). Mass Spectrum (ESI+) m/e = 303 (M+1).

[0218] **Compound 83.** DMF (200 μL) was added to a solution of **82a** (57.23 g, 0.189 mol) and oxalyl chloride (19.8 mL, 0.227 mol) in CH_2Cl_2 (500 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 15 min. and at r.t. for 3 h. The solvent was removed *in vacuo* to provide the acid chloride as an off-white solid (60.3 g). A three-necked 2 liter round-bottomed flask was charged with CuCN (4.19 g, 46.8 mmol) and anhydrous THF (500 mL) and cooled to –25 °C. To this stirred suspension was added a 2M solution of isopropylmagnesium chloride (46.8 mL, 93.5 mmol in THF) dropwise while maintaining an internal temperature between –25 and –22 °C. To this solution was added a solution of the acid chloride (preparation described above) (10 g, 31.2 mmol) in anhydrous THF (50 mL) dropwise while maintaining an internal temperature between –20 and –17 °C. The reaction mixture was stirred at –15 °C for 1 h and quenched with 10% NH_4OH in saturated aqueous NH_4Cl (300 mL). This solution was warmed to r.t. and the layers were separated. The organic layer was washed with 10% NH_4OH in saturated aqueous NH_4Cl (2 ×

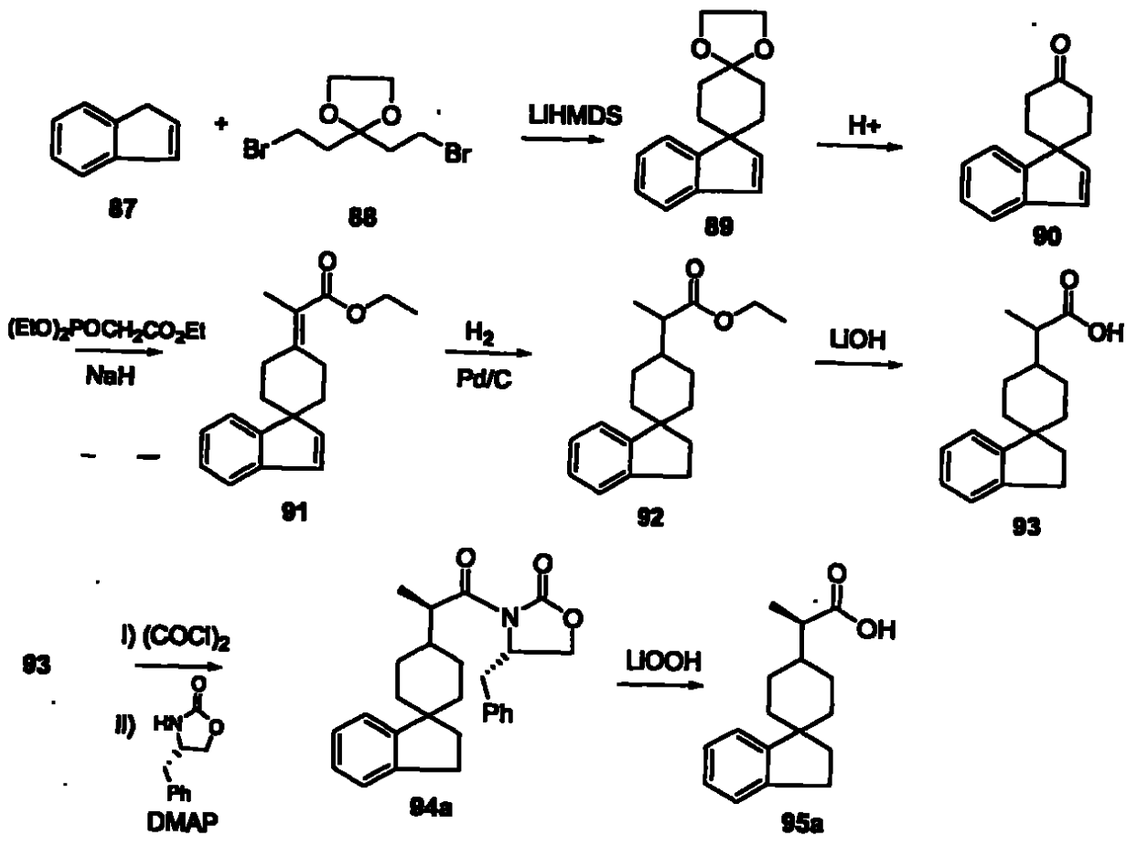
300 mL), brine (1 × 300 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide 83 as an off-white solid (10.08 g). ^{1}H NMR ($CDCl_3$) δ 7.83 (m, 2H), 7.22 (d, J = 8.4 Hz, 1H), 3.72 (s, 3H), 3.54-3.58 (m, 1H), 2.94 (t, J = 7.4 Hz, 2H), 2.30 (d, J = 7.0 Hz, 2H), 2.04 (t, J = 7.4 Hz, 2H), 1.92 (m, 1H), 1.78 (m, 2H), 1.69-1.64 (m, 4H), 1.28 (m, 2H), 1.23 (d, J = 6.8 Hz, 6H). Mass Spectrum (ESI+) m/e = 329 (M+1).

[0219] **Compound 84.** A solution of 83 (5 g, 15.2 mmol) in EtOAc (100 mL) and chloroform (100 mL) was treated with $CuBr_2$ (10 g, 44.8 mmol) and the mixture was heated at reflux for 8 h before being cooled to r.t. The reaction mixture was filtered and washed with EtOAc. The filtrate was washed with water, brine and dried over sodium sulfate. The solvents were removed *in vacuo* and hexane (20 mL) was added. A white solid 84 was formed with stirring and collected by filtration (5 g). Additional 84 (0.76 g) was obtained by crystallization from the mother liquor at 0 °C. ^{1}H NMR ($CDCl_3$) δ 1.25-1.28 (m, 2H), 1.61-1.92 (m, 7H), 2.03-2.06 (m, 8H), 2.29 (d, J = 7.0 Hz, 2H), 2.94 (t, J = 7.4 Hz, 2H), 3.72 (s, 3H), 7.19 (d, J = 8.0 Hz, 1H), 7.99 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H). Mass Spectrum (ESI+) m/e = 407 and 409 (M+1).

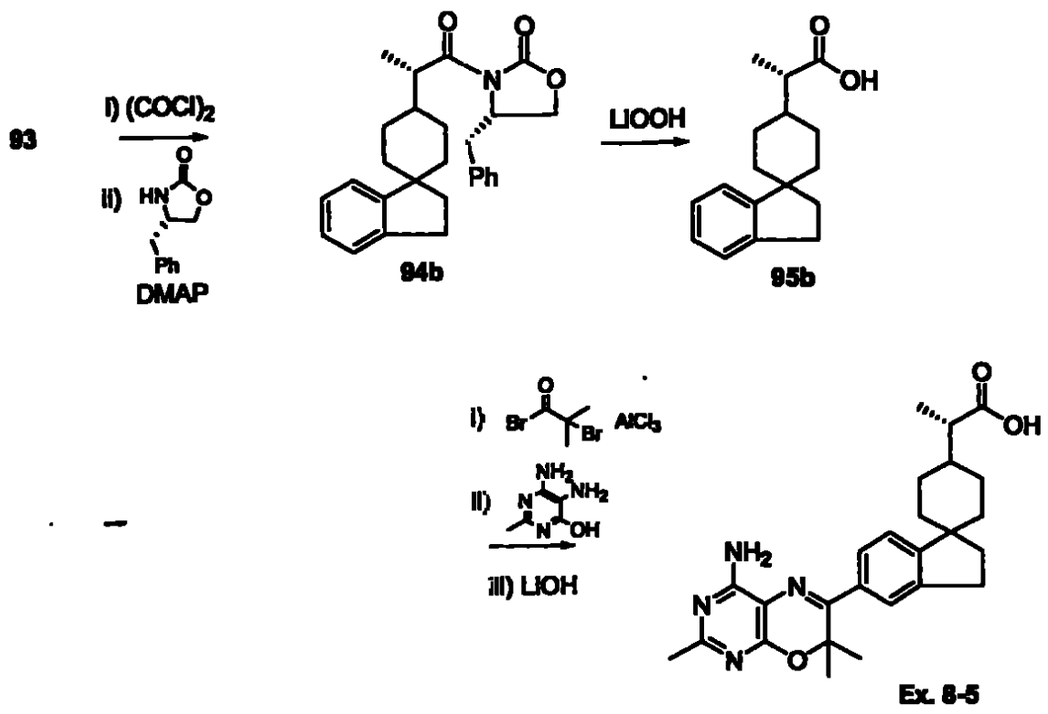
[0220] **Compound 86.** To 84 (0.5 g, 1.23 mmol.) and 4,5-diamino-6-hydroxy-2-trifluoromethylpyrimidine (85, J.A. Barone *et al.*, *J. Med. Chem.*, 1969, 6, 39; P.D. Landauer *et al.*, *J. Chem. Soc.*, 1953, 3721.) (0.26 g, 1.34 mmol) was added methanol (13 mL), 2N HCl (2 mL) and water (5 mL). The mixture was heated at reflux for 24 h, cooled and concentrated *in vacuo*. To the residue was added water (10 mL) and the resulting precipitate was collected by filtration, washed with pentane and dried under vacuum to afford 86 (375 mg) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.18-1.27 (m, 2H), 1.48-1.86 (m, 13H), 1.98 (t, J= 7.3 Hz, 2H), 2.28 (d, J = 7.2 Hz, 2H), 2.89 (t, J = 7.1 Hz, 2H), 3.61 (s, 3H), 7.28 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.58 (s, 1H).

[0221] **Ex. 8-3.** To a stirred solution of 86 (100 mg, 0.199 mmol) in DMF (1 mL) was added anhydrous lithium iodide (670 mg, 5 mmol). The mixture was heated at 125-130 °C for 24 h and poured into water (20 mL). The resulting precipitate was collected by filtration and washed with water. The precipitate was recrystallized from ethanol to afford Ex. 8-3 (70 mg) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.17-1.26 (m, 2H), 1.48-1.82 (m, 16H), 1.98 (t, J= 7.4 Hz, 2H), 2.18 (d, J = 6.8 Hz, 2H), 2.90 (t, J = 7.2 Hz, 2H), 7.28 (d, J = 8.1 Hz, 1H), 7.37 (brs, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.58 (s, 1H), 7.80 (brs, 1H), 12.05 (brs, 1H).

Example 8-4:


87
88
LIHMDS
89
H+
90
(EtO)2POCH2CO2Et
NaH
91
H2
Pd/C
92
LiOH
93
93
I) (COCl)2
II)
Ph
DMAP
94a
LiOOH
95a
I)
II)
III) LiOH
Ex. 8-4

5



[0222] **Compound 89.** A dried 500 mL single-necked round bottom flask was charged with indene 87 (8.91g, 76.65 mmol) and THF (60 mL). The solution was stirred and cooled by an ice bath. To the flask was added lithium bis(trimethylsilyl)amide (153.3 mL, 1.0 M in THF, 153.3 mmol) through a syringe over a period of 30 min. The resulting mixture was stirred at 0 °C for 30 min., and transferred by a cannula to a stirred solution of the dibromoketal 88 (20.0 g, 66.23 mmol) in THF at 0 °C over 30 min. After addition, the reaction mixture was stirred for 2 h at 0 °C and 30 min. at r.t. The solvent was evaporated *in vacuo* and the residue was purified by silica gel chromatography (hexane/EtOAc 25/1 to 15/1; gradient elution) to give compound 89 (15.0 g) as light yellow crystals. ^{1}H NMR ($CDCl_3$) δ 1.43 (d, J = 13.5 Hz, 2H), 1.88-1.99 (m, 4H), 2.20 (d, J = 4.0, 13.0 Hz, 2H), 4.06 (s, 4H), 6.78 (d, J = 6.0, 1H), 6.85 (d, J = 6.0, 1H), 7.20-7.27 (m, 2H), 7.34 (d, J = 7.5, 1H), 7.42 (d, J = 7.5, 1H). Mass Spectrum (ESI+) m/e = 243 (M^++1).

[0223] **Compound 90.** To the solution of 89 (15.0 g, 62 mmol) in MeOH (350 mL) was added 3M H_2SO_4 (60 mL). The reaction mixture was heated at reflux for 7 h under a nitrogen atmosphere. The mixture was cooled to r.t. and the MeOH removed *in vacuo*. The mixture was diluted with ice water and extracted with EtOAc (100 mL x 3), washed with water (25 mL x 2) and brine (20 mL) and dried over $MgSO_4$. Concentration *in vacuo* gave a crude product which was purified by silica gel column chromatography (hexane/EtOAc

20/1) to give compound 90 (10.0g) as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.76 (m, 2H), 2.34 (m, 2H), 2.68 (m, 4H), 6.90 (d, J = 6.0, 1H), 6.95 (d, J = 6.0, 1H), 7.25-7.51 (m, 4H). Mass Spectrum (ESI+) m/e = 199 (M+1)

[0224] **Compound 91.** A suspension of NaH (60% dispersion in mineral oil) (2.45 g, 61.25 mmol) in THF (200 mL) in a 500 mL pre-dried flask was cooled to 0 °C under a nitrogen atmosphere. To the flask was added a solution of triethyl 2-phosphonopropionate (14.60 g, 61.25 mmol) in THF (10 mL) dropwise at 0 °C over 15 min. The mixture was stirred at 0 °C for 15 min. and a solution of 90 (7.8 g, 39.20 mmol) in THF (50 mL) was added through an additional funnel dropwise over 25 min. After addition, the mixture was stirred at r.t. overnight. The reaction was quenched with aqueous saturated NH_4Cl solution and was extracted with EtOAc, washed with water and brine, and dried over $MgSO_4$. Evaporation of solvent gave a crude product which was purified by silica gel column chromatography (hexane/EtOAc 20/1) to give compound 91 (10.0g) as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 7.1 Hz, 3H), 1.50-1.1.60 (m, 2H), 1.98 (s, 3H), 1.95-2.05 (m, 2H), 2.25-2.48 (m, 2H), 2.75-2.90 (m, 1H), 3.10-3.25 (m, 1H), 4.25 (q, J = 7.1 Hz, 2H), 6.81 (d, J = 5.7, 1H), 6.93 (d, J = 5.7, 1H), 7.20-7.36 (m, 4H).

[0225] **Compound 92.** 91 (5.6g, 19.72 mmol) was dissolved in EtOAc (60 mL) and was hydrogenated over palladium (10% on charcoal) using hydrogen gas at an atmospheric pressure for 24 h. The mixture was filtered through celite and the filtrate was concentrated *in vacuo* to give product 92 (5.4 g) as colorless oil which was used directly in the next reaction without further purification. ^{1}H NMR ($CDCl_3$) δ 1.18 (d, J = 7.0 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.61-1.85 (m, 9H), 1.98 (t, J = 7.5 Hz, 2H), 2.31 (m, 1H), 2.89 (t, J = 7.4 Hz, 2H), 4.14-4.19 (m, 2H), 7.05-7.20 (m, 4H).

[0226] **Compound 93.** 92 (2.63 g, 9.21 mmol) was dissolved in MeOH / THF / H_2O (40 mL, 5/2/1). To the above solution was added lithium hydroxide monohydrate (1.93 g, 46.0 mmol) and the mixture was stirred at 50 °C overnight. MeOH was removed *in vacuo* and the reaction mixture was acidified with 2N HCl. The mixture was extracted with EtOAc (25 mL x 3), washed with water, brine and dried over $MgSO_4$. Evaporation of solvent gave a crude product which was purified by silica gel column chromatography (hexane/EtOAc 8/1) to give compound 93 (2.38 g) as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.24 (d, J = 7.02 Hz, 3H), 1.61-1.85 (m, 10H), 1.95-2.0 (m, 2H), 2.3-2.4 (m, 1H), 2.88-2.92 (m, 2H), 7.05-7.20 (m, 4H). Mass Spectrum (ESI+) m/e = 258 (M).

[0227] **Compound 94a and 94b.** To 93 (2.2 g, 8.53 mmol) in CH_2Cl_2 at 0°C under a nitrogen atmosphere was added $(COCl)_2$ (0.82 mL, 9.38 mmol) and a drop of DMF. The reaction was stirred at 0 °C for 1 h. To this generated acid chloride solution was added a solution of (*S*)-(-)-4-benzyl-2-oxazolidione (1.66 g, 9.37 mmol), DMAP (1.09 g, 8.92 mmol) and triethylamine (1.88 mL, 13.49 mmol) in CH_2Cl_2 dropwise at 0 °C under a nitrogen atmosphere. After addition, the mixture was stirred at r.t. for 2h. The reaction was quenched by addition of saturated aqueous NH_4Cl, extracted with EtOAc (25 mL x 3), washed with water (10 mL x 2), brine and dried over $MgSO_4$. Concentration *in vacuo* gave a crude product which was purified by silica gel column chromatography (hexane/EtOAc 19/1 to 10/1) to give compound 94a (926 mg) and 94b (1.27 g). NB: stereochemical assignment of 94a and 94b is arbitrary. Compound 94a: ^{1}H NMR ($CDCl_3$) δ 1.26 (d, J = 6.9 Hz, 3H), 1.61-1.80 (m, 2H), 1.80-1.95 (m, 7H), 1.99 (t, J = 7.3 Hz, 2H), 2.80 (dd, J = 9.6, J = 13.3 Hz, 1H), 2.91 (t, J = 7.4 Hz, 2H), 3.33 (dd, J = 3.2, 13.3 Hz, 1H), 3.71-3.75 (m, 1H), 4.15-4.23 (m, 2H), 4.70-4.78 (m, 1H), 7.05-7.37 (m, 9H). Mass Spectrum (ESI+) m/e = 418 (M+1). $[\alpha]^{26}$ = +54.85 (c = 0.60, CH_2Cl_2). Compound 94b: ^{1}H NMR ($CDCl_3$) δ 1.21 (d, J = 6.9 Hz, 3H), 1.25-1.95 (m, 9H), 2.01 (t, J = 7.4 Hz, 2H), 2.75 (m, 1H), 2.90 (t, J = 7.3 Hz, 2H), 3.32-3.41 (m, 1H), 3.73-3.78 (m, 1H), 4.12-4.22 (m, 2H), 4.73-4.77 (m, 1H), 7.05-7.39 (m, 9H). Mass Spectrum (ESI+) m/e = 418 (M+1). $[\alpha]^{26}$ = +10.12 (c = 0.60, CH_2Cl_2)

[0228] **Compound 95a.** To a stirred solution of 94a (900 mg, 2.16 mmol) in THF (30 mL) and H_2O (10 mL) was added H_2O_2 (30%, 1.8 mL, 17.7 mmol) and lithium hydroxide monohydrate (360 mg, 8.55 mmol) at 0 °C. The reaction was allowed to warm to r.t. overnight and quenched with saturated aqueous Na_2SO_3 solution and acidified with 10% HCl. The mixture was extracted with EtOAc (15mL x 3), washed with water (5 mL x 2), brine and dried over $MgSO_4$. Concentration *in vacuo* gave a crude product which was purified by silica gel column chromatography (hexane/EtOAc 8/1) to give compound 95a (500 mg) as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.24 (d, J = 7.0 Hz, 3H), 1.61-1.85 (m, 10H), 1.95-2.0 (m, 2H), 2.30-2.40 (m, 1H), 2.88-2.92 (m, 2H), 7.05-7.20 (m, 4H). Mass Spectrum (ESI+) m/e = 258 (M)

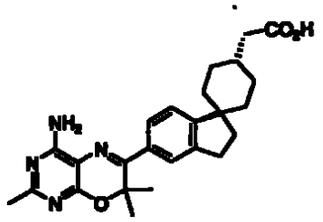
[0229] **Compound 95b.** Compound 95b (*ent*-95a) was prepared from 94b in a similar manner to that described for the conversion of 94a to 95a above.

[0230] **Ex. 8-4.** To a suspension of anhydrous $AlCl_3$ (484 mg, 3.63 mmol) in CH_2Cl_2 (5 mL) was added 2-bromoisobutyryl bromide (0.21 mL, 1.70 mmol) dropwise at 0 °C under a

nitrogen atmosphere. After the mixture was stirred for 5 min., a solution of compound 95a (376 mg, 1.46 mmol) in CH_2Cl_2 (20 mL) was added dropwise. After stirring at 0 °C for 1h, the mixture was poured into ice water and extracted with CH_2Cl_2 (15 mL x 3). The combined organic layer was successively washed with water, saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. To the residue was added 2-methyl-4, 5-diamino-6-hydroxypyrimidine (PD Landauer et al., *J. Chem. Soc.*, 1953, 3721)(250 mg, 1.54 mmol), 1N HCl (5 mL, 5 mmol), water (5 mL) and EtOH (25 mL). The reaction mixture was heated at reflux overnight. The reaction mixture was cooled to r.t. and EtOH was removed by evaporation. The residue was diluted with saturated aqueous NH_4Cl solution and extracted with EtOAc (15 mL x 3). The combined organic layer was successively washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. To the residue was added MeOH / THF / H_2O (15 mL, 1/1/1) and lithium hydroxide monohydrate (200 mg, 4.77 mmol) and the mixture was stirred at 45 °C for 40 h. MeOH was removed *in vacuo* and the residue was acidified with 2N HCl. This mixture was extracted with EtOAc (15 mL x 3), washed with water, brine and dried over $MgSO_4$. Concentration *in vacuo* gave a crude product which was purified by HPLC (reverse phase) to give compound **Ex. 8-4** (65.6 mg) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.07 (d, J = 7.0 Hz, 3H), 1.15-1.35 (m, 1H), 1.50-1.81 (m, 6H), 1.63 (s, 6H), 1.96 (t, J = 7.5 Hz, 2H), 2.21 (m, 1H), 2.34 (s, 3H), 2.45-2.55 (m, 2H), 2.88 (t, J = 7.5, 2H), 7.25 (m, 1H), 7.51-7.54 (m, 4H), 12.0 (bs, 1H). Mass Spectrum (ESI+) m/e = 449 (M+1).

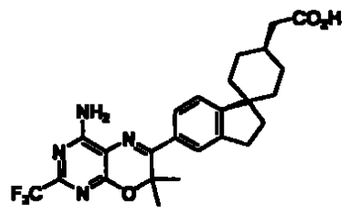
[0231] **Ex 8-5.** Compound **Ex. 8-5** (*ent*-**Ex. 8-4**) was prepared in a similar manner to the preparation of **Ex. 8-4** from 95a above.

Example 8-6:



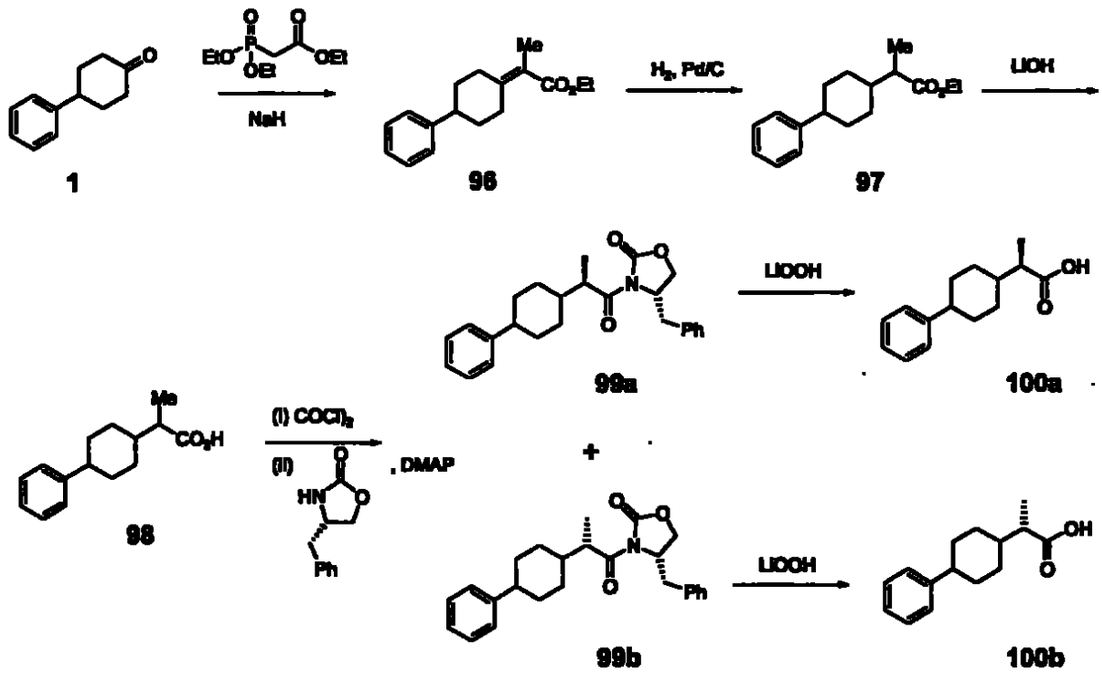
[0232] This compound was obtained in the same manner as in Example 8. ^{1}H NMR (DMSO-d_6) δ 1.14-1.23 (m, 2H), 1.47-1.80 (m, 15H), 1.96 (t, J = 7.3 Hz, 2H), 2.15 (d, J = 7.0 Hz, 2H), 2.32 (s, 3H), 2.87 (t, J = 7.3 Hz, 2H), 7.10 (s, br, 2H), 7.24 (d, J = 7.8 Hz, 1H), 7.43-7.50 (m, 2H).

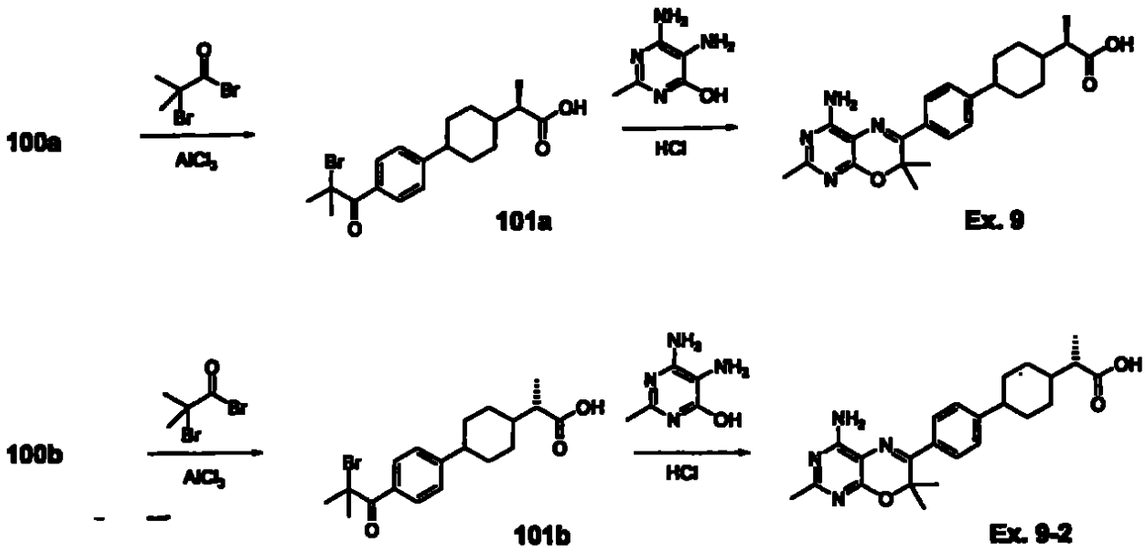
Example 8-7:



[0233] This compound was obtained in the same manner as in Example 8. ^{1}H NMR (DMSO-d_6) δ 1.39-1.45 (m, 2H), 1.47-1.55 (m, 2H), 1.60-1.75 (m, 10H), 1.94 (t, J = 7.2 Hz, 2H), 2.03 (m, 1H), 2.38 (d, J = 7.3 Hz, 2H), 2.87 (t, J = 7.3 Hz, 2H), 7.35 (s, br, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.57 (s, 1H), 7.77 (s, br, 1H).

Example 9





[0234] **Compound 97.** Compound 96 was prepared from 4-phenylcyclohexanone and triethylphosphonopropionate in a similar manner to that described for the conversion of 1 to 2 (Example 2). Compound 97 was prepared from 96 in a similar manner to that described for the conversion of 2 to 3 (Example 2).

[0235] **Compound 98.** To a stirred solution of 97 (2.86 g, 11 mmol) in methanol (83 mL) was added lithium hydroxide (2.62 g, 110 mmol) in water (28 mL). The mixture was heated at reflux for 2 h and allowed to cool to r.t., and the methanol was removed *in vacuo*. The aqueous solution was washed with diethyl ether, acidified to pH 1 with 1N HCl and extracted with diethyl ether (3x). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 98 (2.31 g) as a white solid. ^1H NMR ($CDCl_3$) δ 1.23 (d, J = 7.2 Hz, 3H), 1.29-1.33 (m, 2H), 1.42-1.59 (m, 2H), 1.69-1.80 (m, 2H), 1.85-2.00 (m, 3H), 2.30-2.39 (m, 1H), 2.45-2.60 (m, 1H), 7.21-7.34 (m, 5H).

[0236] **Compounds 99a and 99b.** To a stirred solution of 98 (13.5 g, 58.1 mmol) in DCM (225 mL) was added 3 drops of DMF. The mixture was cooled to 0 °C and oxalyl chloride (5.58 mL, 63.91 mmol) was added dropwise. The mixture was stirred at r.t. for 2 h and added dropwise to a separate vessel containing (*S*)-4-benzyl-2-oxazolidinone (10.81 g, 61 mmol), DMAP (7.1 g, 58.1 mmol), Et_3N (20.24 mL, 145.3 mmol) and DCM (100 mL) at 0 °C. The mixture was allowed to warm to r.t. and stirred at r.t. for 12 h. Water (300 mL) was added. The organic layer was separated and washed with 1N HCl (200 mL), saturated aqueous sodium bicarbonate (200 mL) and brine, and dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel 5-40% EtOAc in

hexane, gradient elution) to provide **99a** (11.48 g) as white crystals and **99b** (10.75 g) as a white foam. NB: the stereochemical assignment of **99a** and **99b** is arbitrary. Compound **99a**: ^{1}H NMR ($CDCl_3$) δ 1.17-1.34 (m, 5H), 1.45-2.01 (m, 7H), 2.49 (tt, J = 12.3 Hz, J = 3.5 Hz, 1H), 2.81 (dd, J = 9.6 Hz, J = 13.2 Hz, 1H), 3.33 (dd, J = 3.2 Hz, J = 13.4 Hz, 1H), 3.74 (quin, J = 7.0 Hz, 1H), 4.19-4.25 (m, 2H), 4.70-4.76 (m, 1H), 7.19-7.39 (m, 10H). Compound **99b**: ^{1}H NMR ($CDCl_3$) δ 1.21 (d, J = 6.9 Hz, 3 H), 1.25-2.02 (m, 9H), 2.51 (tt, J = 12.1 Hz, J = 3.4 Hz, 1H), 2.74 (dd, J = 10.0 Hz, J = 13.2 Hz, 1H), 3.40 (dd, J = 3.4 Hz, J = 13.2 Hz, 1H), 3.78 (quin, J = 6.8 Hz, 1H), 4.12-4.21 (m, 2H), 4.72-4.79 (m, 1H), 7.19-7.39 (m, 10H).

[0237] **Compound 100a.** To a stirred solution of **99a** (10.48 g, 26.8 mmol) in THF (400 mL) and water (125 mL) at 0 °C was added lithium hydroxide (1.28 g, 53.6 mmol) and 3% hydrogen peroxide (10.7 mL). The mixture was stirred at 0 °C for 75 min. and an aqueous solution of sodium sulfite (14.75 g in 80 mL of water) was added followed by 0.5 M aqueous sodium bicarbonate (270 mL). The aqueous layer was washed with DCM and acidified to pH 1 with 5N HCl and extracted with EtOAc. The ethyl acetate layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford **100a** (1 g) as a white solid.

[0238] Additional material could be obtained from the DCM layer. ^{1}H NMR ($CDCl_3$) δ 1.22 (d, J = 7.2 Hz, 3H), 1.23-1.33 (m, 2H), 1.50-1.56 (m, 2H), 1.58-1.65 (m, 1H), 1.87-2.01 (m, 4H), 2.38 (quin, J = 6.8 Hz, 1H), 2.50 (tt, J = 3.2 Hz, J = 12.0 Hz, 1H), 7.18-7.33 (m, 5H).

[0239] **Compound 100b.** Compound **100b** (*ent*-**100a**) was prepared from **99b** in a similar manner to the preparation of **100a** from **99a** above.

[0240] **Compound 101a.** Compound **101a** was prepared from **100a** in a similar manner to that described for the conversion of **3** to **4** (Example 2). ^{1}H NMR ($CDCl_3$) δ 1.23 (d, J = 7.2 Hz, 3H), 1.29-1.33 (m, 2H), 1.42-1.59 (m, 2H), 1.69-1.80 (m, 2H), 1.85-2.00 (m, 3H), 2.30-2.39 (m, 1H), 2.45-2.60 (m, 1H), 7.21-7.34 (m, 5H).

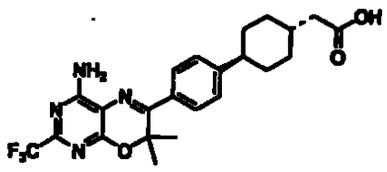
[0241] **Compound 101b.** Compound **101b** (*ent*-**101a**) was prepared from **100b** in a similar manner to the preparation of **101a** from **100a** above.

[0242] **Ex. 9.** **Ex. 9** was prepared from **101a** and 4,5-diamino-6-hydroxy-2-methylpyrimidine (P.D. Landauer *et al.*, *J. Chem. Soc.*, 1953, 3721.) in a similar manner to that described for the conversion of **4** to **Ex. 2**. ^{1}H NMR ($CDCl_3$) δ 1.24 (d, J = 6.8 Hz, 3H),

1.25-1.30 (m, 2H), 1.48-1.59 (m, 3H), 1.71 (s, 6H), 1.91-2.00 (m, 4H), 2.36-2.40 (m, 1H), 2.46 (s, 3H), 2.51-2.57 (m, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H). Mass Spectrum (ESI+) m/e = 423.3 (M+1).

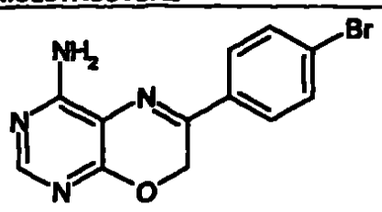
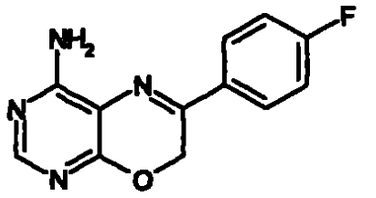
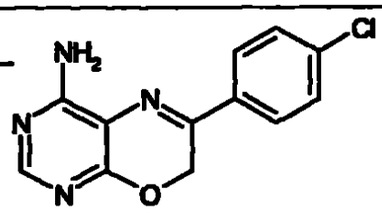
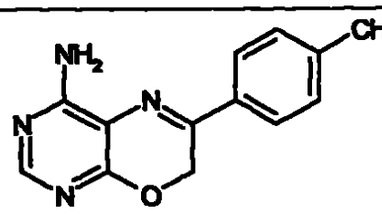
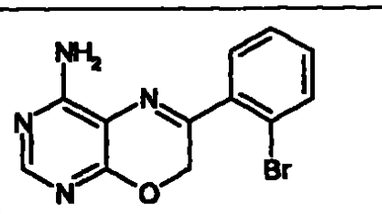
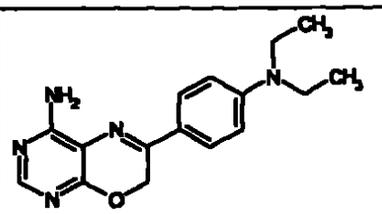
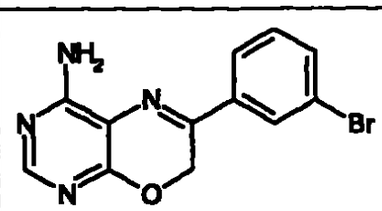
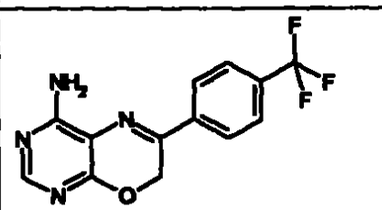
[0243] Ex. 9-2. Ex. 9-2 (*ent*-Ex. 9) was prepared from 101b in a similar manner to the preparation of Ex. 9 from 101a above.

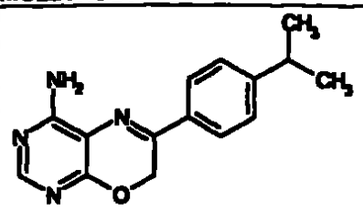
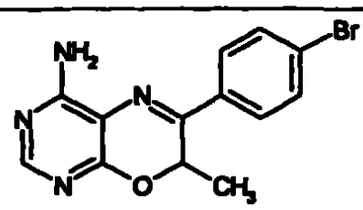
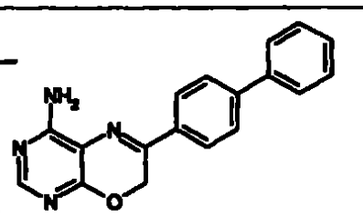
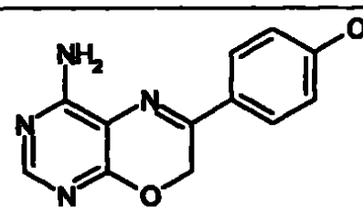
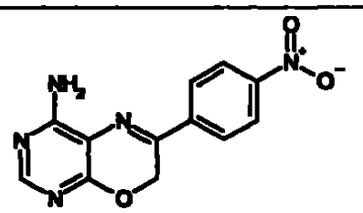
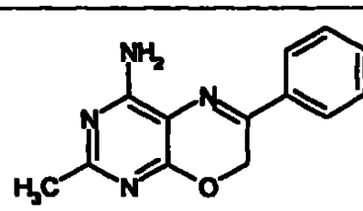
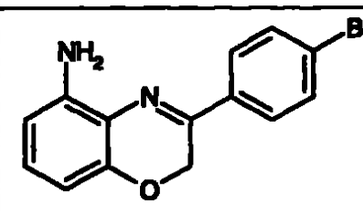
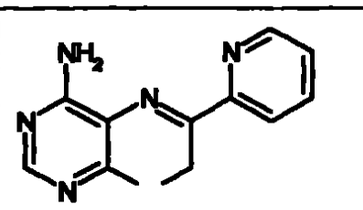
Example 9-3:

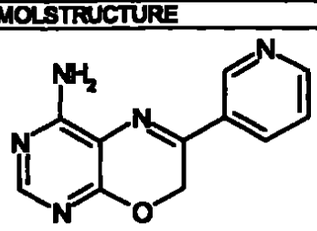
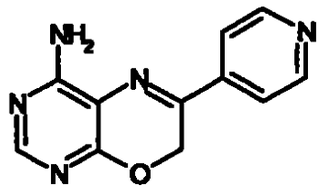
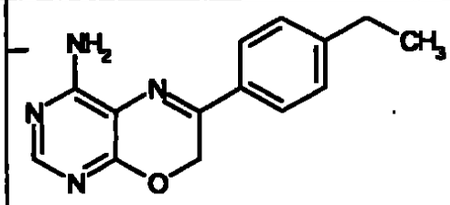
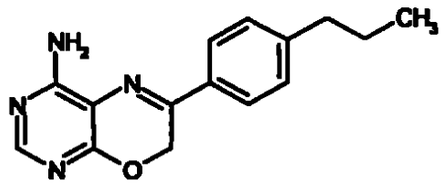
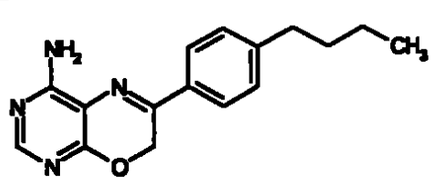
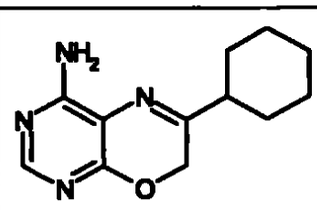
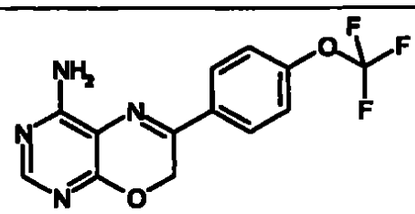
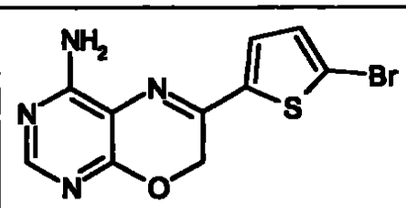


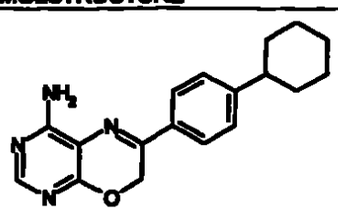
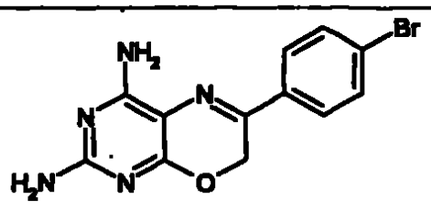
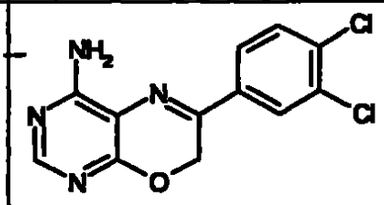
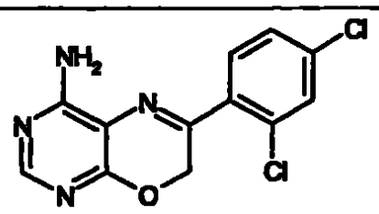
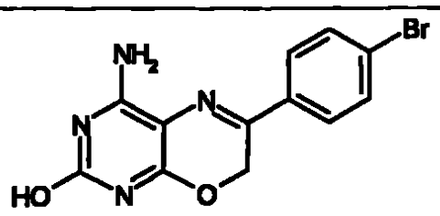
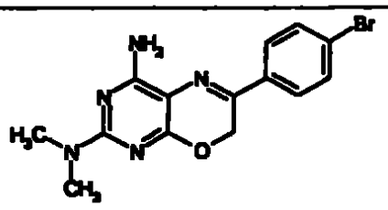
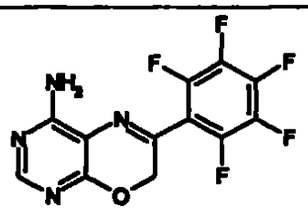
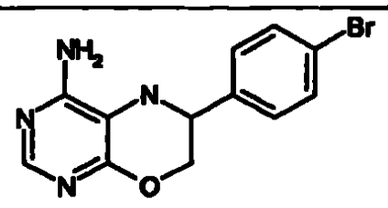
[0244] This compound was obtained in the same manner as in Example 9. ^{1}H NMR (DMSO-d_6) δ 1.10-1.20 (m, 2H), 1.42-1.90 (m, 13H), 2.17 (d, J = 6.8 Hz, 2H), 2.45-2.60 (m, 1H), 7.34 (d, J = 8 Hz, 2H), 7.36 (brs, 1H), 7.71 (d, J = 8Hz, 2H), 7.74 (brs, 1H), 12.04 (brs, 1H).

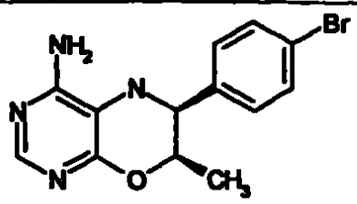
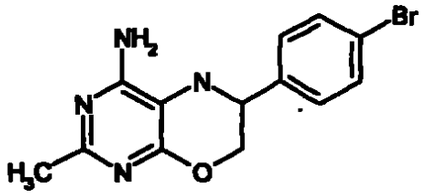
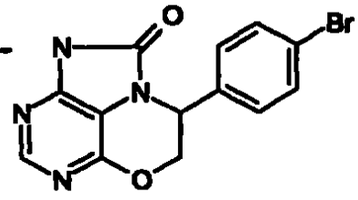
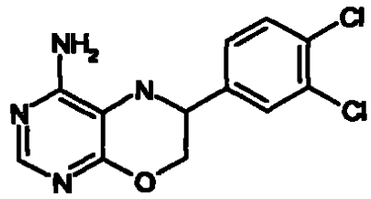
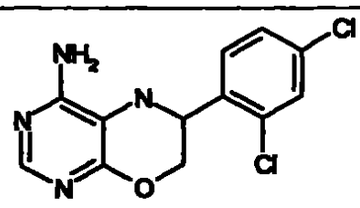
[0245] The compounds provided in Table 10 were prepared by combinations of the methods provided above.

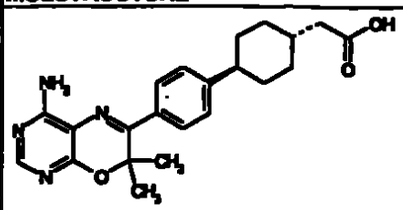
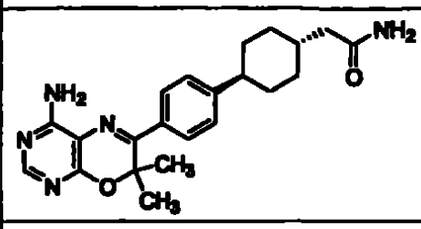
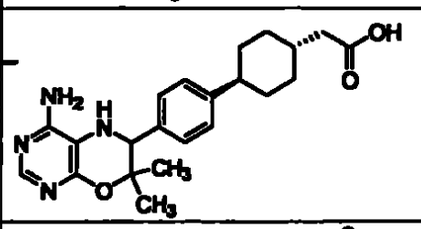
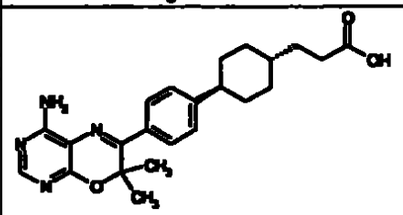
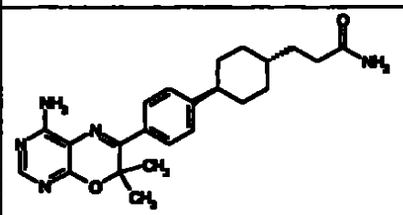
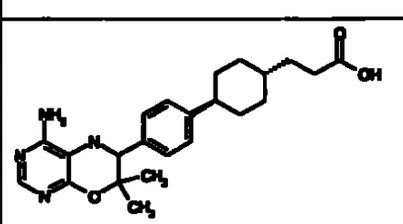
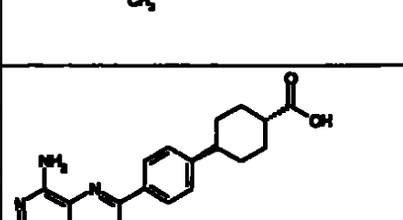
New Ex. No.	MOLSTRUCTURE	m.p	NMR(δ)	solvent
1		>200	5.44(s, 2H), 7.10(brs, 2H), 7.69(d, 2H, J=8.6Hz), 7.93(s, 1H), 8.03(d, 2H, J=8.6Hz).	DMSO-d6, 400MHz
1-2		>220	5.46(s, 2H), 7.08(brs, 2H), 7.35(t, 2H, J=7.5Hz), 7.94(s, 1H), 8.15-8.19(m, 2H)	DMSO-d6, 400
1-3		>220	5.46(s, 2H), 7.12(brs, 2H), 7.57(d, 2H, J=8.0Hz), 7.94(s, 1H), 8.13(d, 2H, J=8.0Hz)	DMSO-d6, 400
1-4		217-219	2.39(s, 3H), 5.43(s, 2H), 7.03(brs, 2H), 7.32(d, 2H, J=8.0Hz), 7.93(s, 1H), 7.99(d, 2H, J=8.0Hz)	DMSO-d6, 400
1-5			5.22(s, 2H), 7.02(brs, 2H), 7.45(t, 1H, J=8.0Hz), 7.53(t, 1H, J=4.5Hz), 7.84(d, 1H, J=8.0Hz), 7.76(d, 1H, J=8.0Hz), 7.99(s, 1H)	DMSO-d6, 400
1-6		208dec.	1.14(t, 6H, J=8.0Hz), 3.44(q, 4H, J=5.0Hz), 5.34(s, 2H), 6.72(d, 2H, J=8.0Hz), 6.84(brs, 2H), 7.88(s, 1H), 7.90(d, 2H, J=9.0Hz)	DMSO-d6, 400
1-7		>220	5.45(s, 2H), 7.19(brs, 2H), 7.46(t, 1H, J=8.0Hz), 7.72(d, 1H, J=8.0Hz), 7.95(s, 1H), 8.01(d, 1H, J=8.0Hz), 8.39(s, 1H)	DMSO-d6, 400
1-8		>220	5.51(s, 2H), 7.19(brs, 2H), 7.86(d, 2H, J=8.0Hz), 7.96(s, 1H), 8.30(d, 2H, J=8.0Hz)	DMSO-d6, 400

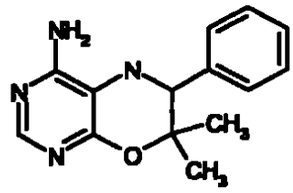
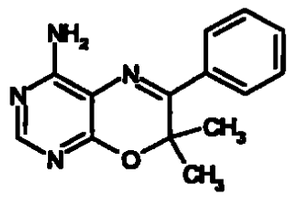
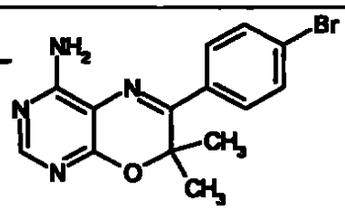
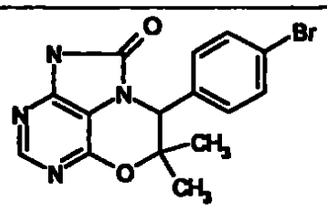
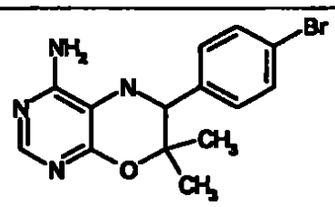
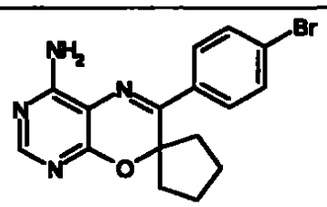
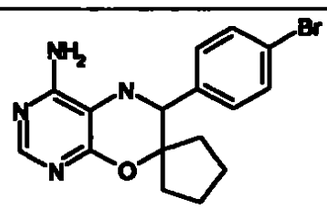
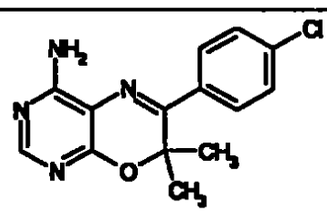
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
1-9		176-178	1.23(d, 6H, J=6.0Hz), 2.93-3.00(m, 1H), 5.42(s, 2H), 7.01(brs, 2H), 7.39(d, 2H, J=6.0Hz), 7.92(s, 1H), 7.99(d, 2H, J=6.0Hz)	DMSO-d6, 400
1-10		222 - 224	1.33(d, 3H, J=6.0Hz), 5.09(q, 1H, J=6.0Hz), 7.14(brs, 2H), 7.69(d, 2H, J=6.0Hz), 7.85(s, 1H), 8.09(d, 2H, J=6.0Hz)	DMSO-d6, 400
1-11		>250	5.49(s, 2H), 7.08(brs, 2H), 7.39-7.43(m, 1H), 7.49-7.52(m, 2H), 7.76-7.81(m, 4H), 7.93(s, 1H), 8.18(d, 2H, J=6.0Hz)	DMSO-d6, 400
1-12		191 - 193	3.84(s, 3H), 5.40(s, 2H), 6.98(brs, 2H), 7.03(d, 2H, J=6.0Hz), 7.90(s, 1H), 8.05(d, 2H, J=6.0Hz)	DMSO-d6, 400
1-13		>250	5.52(s, 2H), 7.25(brs, 2H), 7.96(s, 1H), 8.30(d, 2H, J=6.0Hz), 8.34(d, 2H, J=6.0Hz)	DMSO-d6, 400
1-14		>220	2.25(s, 3H), 5.40(s, 2H), 7.05(brs, 2H), 7.70(d, 2H, J=9.0Hz), 8.03(d, 2H, J=9.0Hz)	DMSO-d6, 300
1-15		75 - 77	5.05(s, 2H), 5.58(brs, 2H), 6.08(dd, 1H, J=1.1, 8.0 Hz), 6.32(dd, 1H, J=1.1, 8.0 Hz), 6.85(t, 1H, J=8.0 Hz), 7.69(d, 2H, J=8.6 Hz), 8.04(d, 2H, J=8.6 Hz).	DMSO-d6, 300MHz
1-16		215	5.86(s, 2H), 7.22(br, 2H), 7.51-7.55(m, 1H), 7.95-8.00(m, 2H), 8.52-8.55(m, 1H), 8.85-8.87(m, 1H)	DMSO-d6, 300

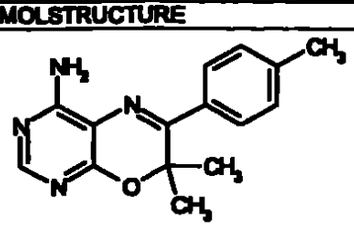
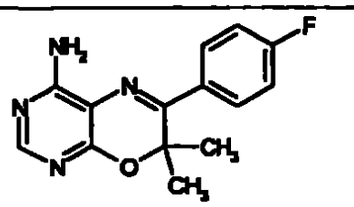
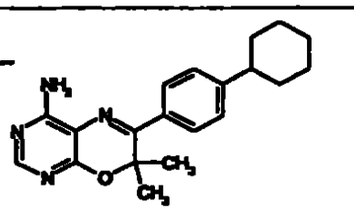
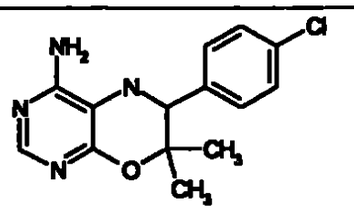
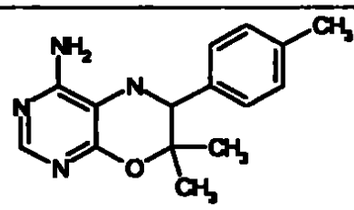
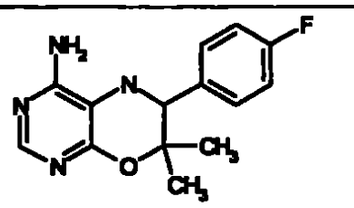
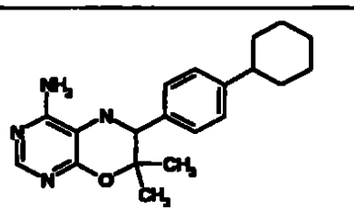
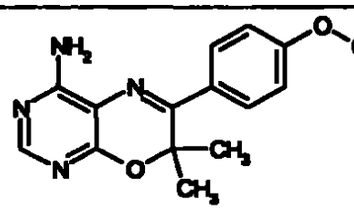
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
1-17		>220	5.49(s, 2H), 7.21(brs, 2H), 7.51-7.55(m, 1H), 7.94(s, 1H), 8.44-8.48(m, 1H), 8.68-8.70(m, 1H), 9.27(s, 1H)	DMSO-d6, 300
1-18		>220	5.48(s, 2H), 7.28(br, 2H), 7.96(s, 1H), 8.01(d, 2H, J=6.0Hz), 8.73(d, 2H, J=6.0Hz)	DMSO-d6, 300
1-19		191 - 193	1.21(t, 3H, J=7.5Hz), 2.68(q, 2H, J=7.0Hz), 5.43(s, 2H), 7.07(brs, 2H), 7.34(d, 2H, J=9.0Hz), 7.92(s, 1H), 8.01(d, 2H, J=9.0Hz)	DMSO-d6, 300
1-20		189 - 192	0.90(t, 3H, J=7.5Hz), 1.56-1.68(m, 2H), 2.60-2.65(m, 2H), 5.43(s, 2H), 7.07(brs, 2H), 7.32(d, 2H, J=9.0Hz), 7.92(s, 1H), 8.01(d, 2H, J=9.0Hz)	DMSO-d6, 300
1-21		183 - 186	0.91(t, 3H, J=7.5Hz), 1.27-1.37(m, 2H), 1.53-1.63(m, 2H), 2.62-2.67(m, 2H), 5.43(s, 2H), 7.08(brs, 2H), 7.32(d, 2H, J=9.0Hz), 7.92(s, 1H), 8.00(d, 2H, J=9.0Hz)	DMSO-d6, 400
1-22		142	1.14-1.45(m, 5H), 1.61-1.85(m, 5H), 2.23-2.30(m, 1H), 4.89(s, 2H), 6.74(brs, 2H), 7.87(s, 1H)	DMSO-d6, 400
1-23		209 - 212	5.47(s, 2H), 7.17(brs, 2H), 7.49(d, 2H, J=8.0Hz), 7.94(s, 1H), 8.22(d, 2H, J=8.0Hz)	DMSO-d6, 300
1-24			5.35(s, 2H), 6.95(brs, 2H), 7.35(d, 2H, J=8.0Hz), 7.52(d, 2H, J=3.0Hz), 7.92(s, 1H)	DMSO-d6, 300

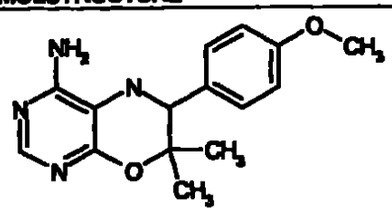
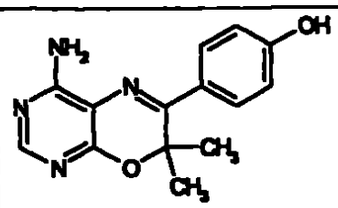
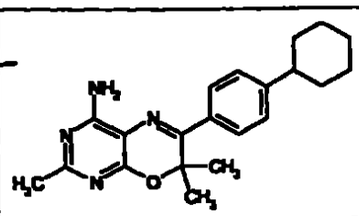
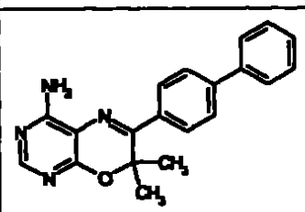
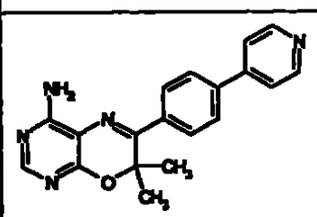
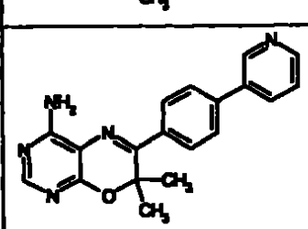
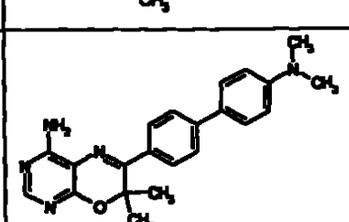
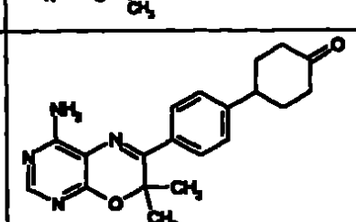
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
1-25		219 - 221	1.23-1.51(m, 5H), 1.69-1.85(m, 5H), 2.55-2.63(m, 1H), 5.43(s, 2H), 7.08(brs, 2H), 7.92(s, 1H), 8.00(d, 2H, J=9.0Hz)	DMSO-d6, 300
1-26		>220	5.25(s, 2H), 6.24(brs, 2H), 6.55(brs, 2H), 7.83(d, 2H, J=12.0Hz), 7.92(d, 2H, J=12.0Hz)	DMSO-d6, 400
1-27		>220	5.45(s, 2H), 7.29(brs, 2H), 7.77(d, 1H, J=9.0Hz), 7.94(s, 1H), 8.02(d, 1H, J=9.0Hz), 8.46(s, 1H)	DMSO-d6, 300
1-28		218 - 220	5.22(s, 2H), 7.17(brs, 2H), 7.57-7.60(m, 1H), 7.75-7.79(m, 2H), 7.99(s, 1H)	DMSO-d6, 300
1-29		>220	5.35(s, 2H), 7.18(brs, 2H), 7.85(d, 2H, J=9.0Hz), 7.92(d, 2H, J=8.0Hz), 10.87(brs, 1H)	DMSO-d6, 400
1-30		>220	3.04(s, 6H), 5.27(s, 2H), 6.73(brs, 2H), 7.83(d, 2H, J=8.0Hz), 7.94(d, 2H, J=8.0Hz)	DMSO-d6, 400
1-31		190 - 192	5.17(s, 2H), 8.01(s, 1H)	DMSO-d6, 300
1-32		>200	4.07(dd, 1H, J=7.8, 10.7 Hz), 4.33(dd, 1H, J=1.8, 10.7 Hz), 4.48(m, 1H), 5.19(brs, 1H), 6.27(brs, 2H), 7.40(d, 2H, J=8.6 Hz), 7.58(s, 1H), 7.80(d, 2H, J=8.6 Hz).	DMSO-d6, 400MHz

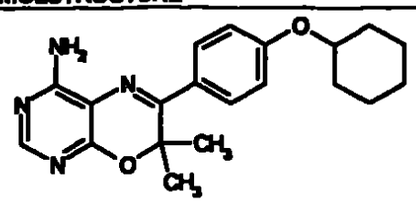
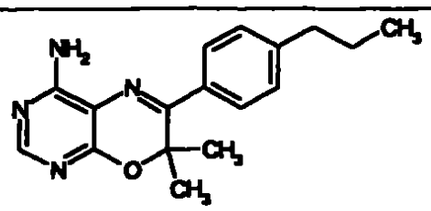
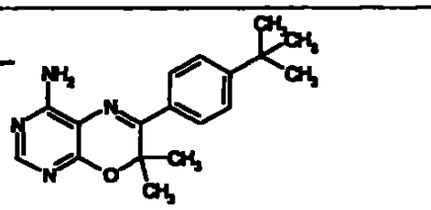
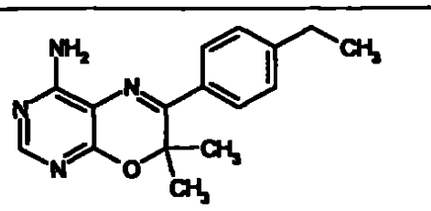
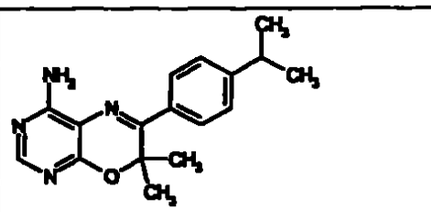
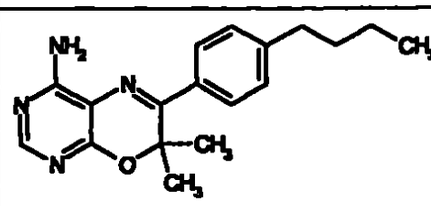
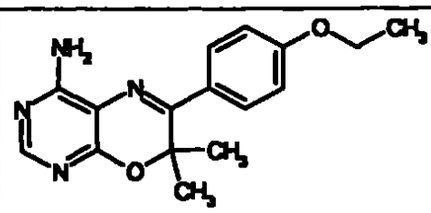
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
1-33			0.99(d, 3H, J=6.0Hz), 4.54(brs, 2H), 5.38(br, 1H), 6.38(br, 2H), 7.28(d, 2H, J=6.0Hz), 7.58(d, 2H, J=9.0Hz), 7.65(s, 1H)	DMSO-d6, 300
1-34		232 - 233	2.16(s, 3H), 4.03-4.08(m, 1H), 4.28-4.32(m, 1H), 4.42-4.45(m, 1H), 4.99(brs, 1H), 6.19(brs, 2H), 7.40(d, 2H, J=6.0Hz), 7.58(d, 2H, J=9.0Hz)	DMSO-d6, 400
1-35		>220	4.56-4.73(m, 2H), 5.46-5.49(m, 1H), 7.28(d, 2H, J=9.0Hz), 7.60(d, 2H, J=9.0Hz), 8.30(s, 1H), 11.94(brs, 1H)	DMSO-d6, 300
1-36		198 - 200	4.08-4.15(m, 1H), 4.34-4.38(m, 1H), 4.54(brs, 1H), 5.23(brs, 1H), 6.35(brs, 2H), 7.45(d, 1H, J=12.0Hz), 7.83(s, 1H), 7.89(d, 1H, J=9.0Hz), 7.74(s, 1H)	DMSO-d6, 300
1-37		>220	4.02-4.09(m, 1H), 4.34-4.38(m, 1H), 4.80(brs, 1H), 5.28(brs, 1H), 6.35(brs, 2H), 7.51(s, 2H), 7.84(s, 1H), 7.70(s, 1H)	DMSO-d6, 300

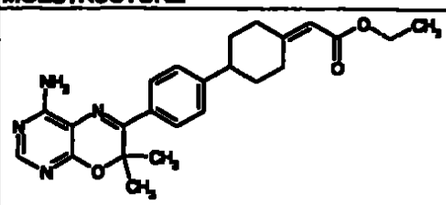
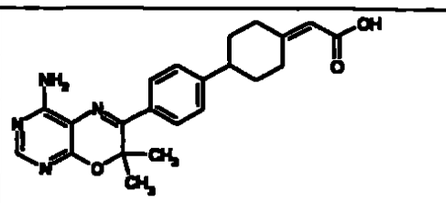
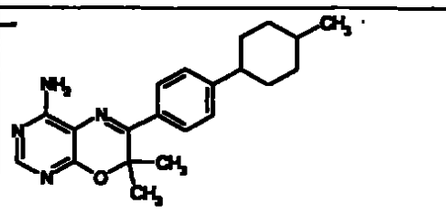
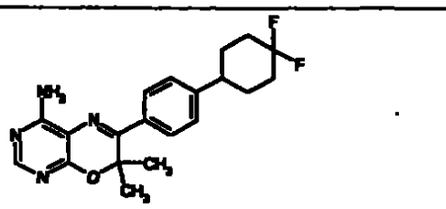
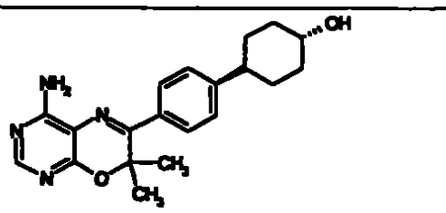
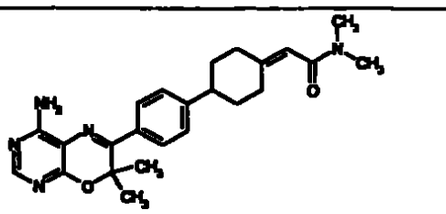
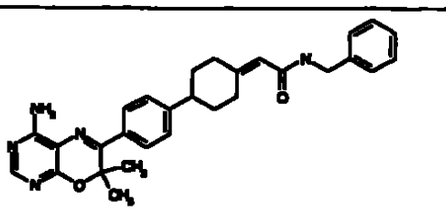
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2		>270	1.07-1.21(m, 2H), 1.42-1.84(m, 13H), 2.15(d, 2H, J=6.0Hz), 2.53-2.56(m, 1H), 6.97(brs, 2H), 7.31(d, 2H, J=9.0Hz), 7.85(d, 2H, J=9.0Hz), 7.95(s, 1H), 11.96(brs, 1H)	DMSO-d6, 300
2-2		224 - 226	1.02-1.17(m, 2H), 1.4-1.53(m, 2H), 1.61(s, 6H), 1.66-1.87(m, 5H), 1.98(d, 2H, J=7.12Hz), 2.53(m, 1H), 6.87(br, 1H), 6.89(br, 2H), 7.21(br, 1H), 7.3(d, 2H, J=8.12Hz), 7.83(d, 2H, J=8.12Hz), 7.94(s, 1H)	DMSO-d6, 400
2-3		273 - 279	1.03-1.22(m, 5H), 1.4-1.49(m, 2H), 1.7-1.82(m, 5H), 2.14(d, 2H, J=6.93Hz), 2.54(m, 1H), 4.11(br, 1H), 5.27(br, 1H), 6.23(br, 2H), 7.25(d, 2H, J=8.07Hz), 7.36(d, 2H, J=8.04Hz), 7.61(s, 1H), 11.75(br, 1H)	DMSO-d6, 300
2-4		>250	1.04-1.09(m, 2H), 1.43(m, 1H), 1.43-1.50(m, 4H), 1.60(s, 6H), 1.83(brd, 4H, J=11.4 Hz), 2.25(t, 2H, d=7.7 Hz), 2.50(m, 1H), 6.86(brs, 2H), 7.29(d, 2H, J=8.3 Hz), 7.83(d, 2H, J=8.3 Hz), 7.94(s, 1H), 11.84(brs, 1H).	DMSO-d6, 400MHz
2-5		244 - 246	1.04-1.08(m, 2H), 1.29(m, 1H), 1.40-1.49(m, 4H), 1.60(s, 6H), 1.83(brd, 4H, J=10.2 Hz), 2.09(t, 2H, d=7.4 Hz), 2.50(m, 1H), 6.60(brs, 1H), 6.86(brs, 2H), 7.20(brs, 1H), 7.29(d, 2H, J=8.3 Hz), 7.83(d, 2H, J=8.3 Hz), 7.94(s, 1H).	DMSO-d6, 400MHz
2-6		>250	1.04-1.09(m, 2H), 1.08(s, 3H), 1.22(s, 3H), 1.32(m, 1H), 1.43-1.48(m, 4H), 1.83(brd, 4H, J=10.7 Hz), 2.24(t, 2H, d=7.7 Hz), 2.50(m, 1H), 4.11(s, 1H), 5.26(s, 1H), 6.22(brs, 2H), 7.23(d, 2H, J=8.1 Hz), 7.35(d, 2H, J=8.1 Hz), 7.82(s, 1H), 11.73(brs, 1H).	DMSO-d6, 400MHz
2-7		>250	1.42-1.55(m, 4H), 1.60(s, 6H), 1.81-1.91(m, 2H), 1.95-2.08(m, 2H), 2.23-2.33(m, 1H), 2.52-2.60(m, 1H), 6.90(br, 2H), 7.30(d, 2H, J=8.1Hz), 7.84(d, 2H, J=8.1Hz), 7.95(s, 1H)	DMSO-d6, 400MHz

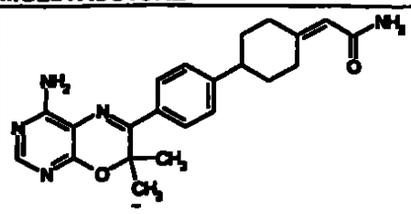
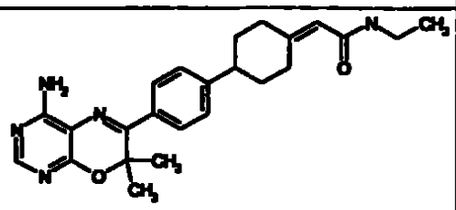
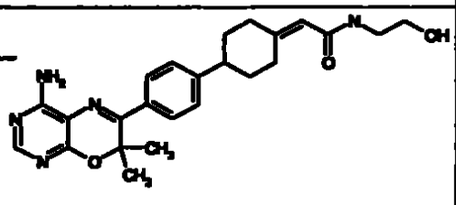
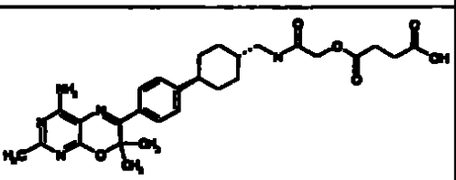
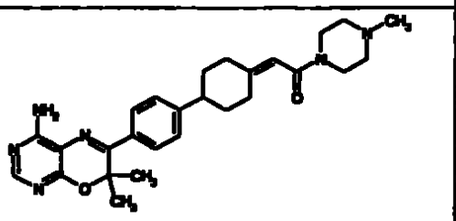
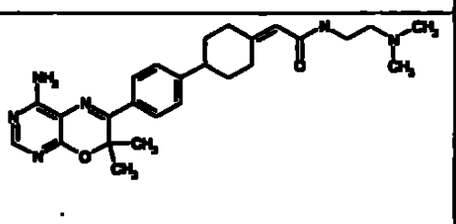
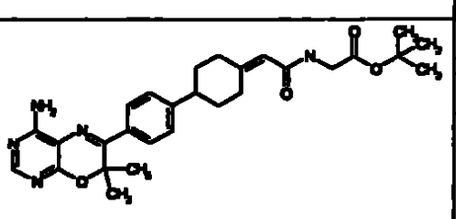
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-8		>220	1.07(s, 3H), 1.23(s, 3H), 4.17(brs, 1H), 5.31(brs, 1H), 6.26(brs, 2H), 7.35-7.47(m, 5H), 7.83(s, 1H)	DMSO-d6, 300
2-9		189 - 190	1.60(s, 6H), 6.93(brs, 2H), 7.44-7.50(m, 3H), 7.69-7.71(m, 2H), 7.96(s, 1H)	DMSO-d6, 400
2-10		201 - 203	1.60(s, 6H), 7.03(brs, 2H), 7.65(d, 2H, J=9.0Hz), 7.70(d, 2H, J=9.0Hz), 7.96(s, 1H)	DMSO-d6, 300
2-11		>220	1.22(s, 3H), 1.47(s, 3H), 5.38(s, 2H), 6.99(d, 2H, J=8.0Hz), 7.55(d, 2H, J=8.0Hz), 8.35(s, 1H), 11.94(brs, 1H)	DMSO-d6, 400
2-12		>220	1.05(s, 3H), 1.23(s, 3H), 4.20(brs, 1H), 5.33(brs, 1H), 6.26(brs, 2H), 7.40(d, 2H, J=9.0Hz), 7.80(d, 2H, J=8.0Hz), 7.83(s, 1H)	DMSO-d6, 300
2-13		184 - 186	1.78-1.86(m, 2H), 2.01-2.08(m, 1H), 2.13-2.19(m, 1H), 7.05(brs, 2H), 7.61(d, 2H, J=8.0Hz), 7.86(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 400
2-14		226 - 233	1.29-1.76(m, 4H), 4.37(brs, 1H), 5.51(brs, 1H), 6.23(brs, 2H), 7.27(d, 2H, J=8.0Hz), 7.55(d, 2H, J=8.0Hz), 7.83(s, 1H)	DMSO-d6, 300
2-15		210 - 211	1.60(s, 6H), 7.05(brs, 2H), 7.52(d, 2H, J=9.0Hz), 7.77(d, 2H, J=9.0Hz), 7.96(s, 1H)	DMSO-d6, 300

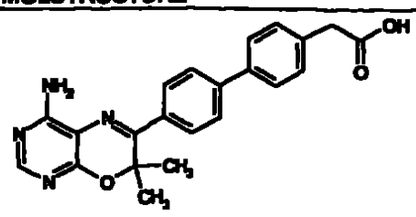
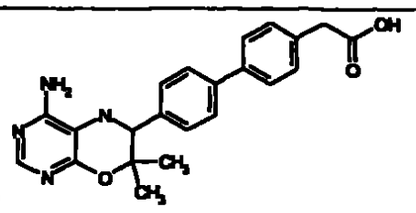
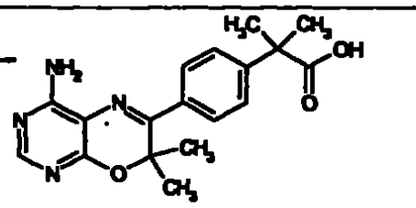
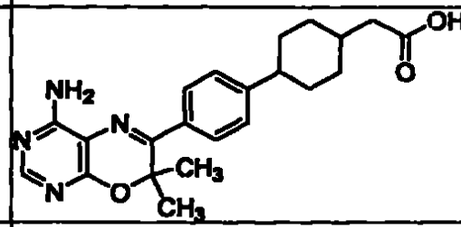
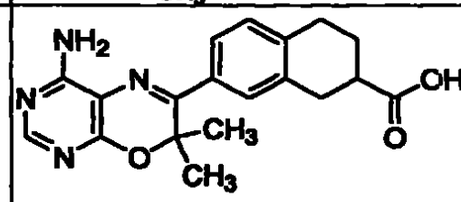
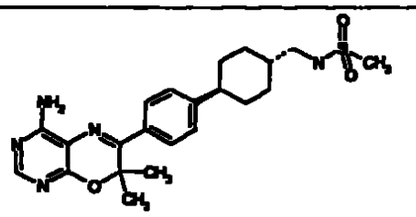
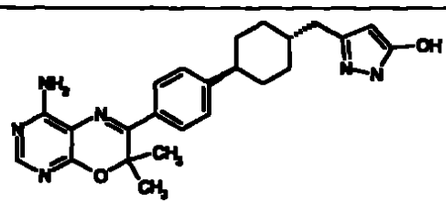
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-16		161 - 162	1.60(s, 6H), 2.36(s, 3H), 6.97(brs, 2H), 7.27(d, 2H, J=9.0Hz), 7.83(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-17		189 - 190	1.60(s, 6H), 7.01(brs, 2H), 7.29(dd, 2H, J=9.0, 9.0Hz), 7.81(dd, 2H, J=9.0, 9.0Hz), 7.96(s, 1H)	DMSO-d6, 300
2-18		186 - 187	1.21-1.47(m, 5H), 1.60(s, 6H), 1.70-1.82(m, 5H), 2.54-2.58(m, 1H), 6.89(brs, 2H), 7.29(d, 2H, J=8.0Hz), 7.84(d, 2H, J=9.0Hz), 7.94(s, 1H)	DMSO-d6, 400
2-19		>230	1.05(s, 3H), 1.23(s, 3H), 4.21(brs, 1H), 5.33(brs, 1H), 6.28(brs, 2H), 7.46(s, 4H), 7.83(s, 1H)	DMSO-d6, 300
2-20		>230	1.08(s, 3H), 1.21(s, 3H), 2.31(s, 3H), 4.12(brs, 1H), 5.28(brs, 1H), 6.27(brs, 2H), 7.20(d, 2H, J=8.0Hz), 7.34(d, 2H, J=9.0Hz), 7.82(s, 1H)	DMSO-d6, 300
2-21		>230	1.08(s, 3H), 1.23(s, 3H), 4.20(brs, 1H), 5.28(brs, 1H), 6.22(brs, 2H), 7.22(dd, 2H, J=8.0, 8.0Hz), 7.48(dd, 2H, J=8.0, 8.0Hz), 7.83(s, 1H)	DMSO-d6, 400
2-22		>230	1.08(s, 3H), 1.22(s, 3H), 1.26-1.46(m, 5H), 1.69-1.83(m, 5H), 2.47-2.54(m, 1H), 4.11(brs, 1H), 5.28(brs, 1H), 6.25(brs, 2H), 7.25(d, 2H, J=9.0Hz), 7.37(d, 2H, J=9.0Hz), 7.81(s, 1H)	DMSO-d6, 300
2-23		183 - 184	1.61(s, 6H), 3.82(s, 3H), 6.87(brs, 2H), 6.99(d, 2H, J=8.0Hz), 7.71(d, 2H, J=8.0Hz), 7.94(s, 1H)	DMSO-d6, 400

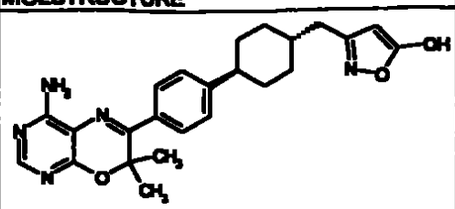
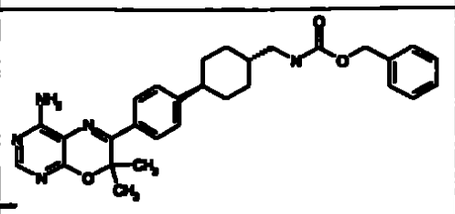
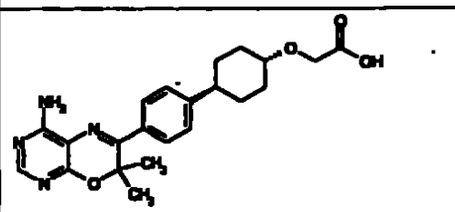
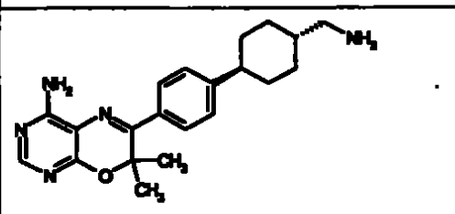
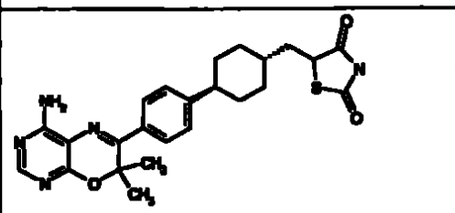
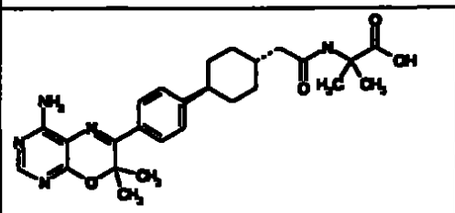
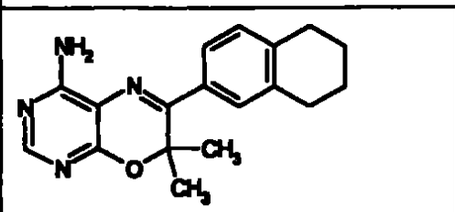
New Ex. No.	MOLSTRUCTURE	m.p	NMR(δ)	solvent
2-24		225 - 226	1.08(s, 3H), 1.21(s, 3H), 3.76(s, 3H), 4.11(brs, 1H), 5.23(brs, 1H), 6.26(brs, 2H), 6.99(d, 2H, J=9.0Hz), 7.38(d, 2H, J=9.0Hz), 7.62(s, 1H)	DMSO-d6, 300
2-25		245 - 246	1.80(s, 6H), 6.82(d, 2H, J=9.0Hz), 6.91(brs, 2H), 7.62(d, 2H, J=6.0Hz), 7.93(s, 1H), 9.94(s, 1H)	DMSO-d6, 300
2-26		226 - 227	1.19-1.46(m, 5H), 1.58(s, 6H), 1.69-1.82(m, 5H), 2.25(s, 3H), 2.52-2.58(m, 1H), 6.86(brs, 2H), 7.29(d, 2H, J=9.0Hz), 7.63(d, 2H, J=9.0Hz)	DMSO-d6, 300
2-27		218 - 219	1.66(s, 6H), 7.02(brs, 2H), 7.39-7.53(m, 3H), 7.73-7.77(m, 4H), 7.83-7.86(m, 2H), 7.97(s, 1H)	DMSO-d6, 300
2-28		>250	1.65(s, 6H), 6.97(brs, 2H), 7.77(d, 2H, J=3.0Hz), 7.88(s, 4H), 7.97(s, 1H), 8.68(d, 2H, J=3.0Hz)	DMSO-d6, 300
2-29		231 - 232	1.66(s, 6H), 7.02(brs, 2H), 7.51-7.55(m, 1H), 7.83(d, 2H, J=8.0Hz), 7.88(d, 2H, J=9.0Hz), 7.98(s, 1H), 8.14-8.18(m, 1H), 8.61-8.63(m, 1H), 8.97-8.99(m, 1H)	DMSO-d6, 300
2-30		210 - 211	1.65(s, 6H), 2.96(s, 6H), 6.83(d, 2H, J=9.0Hz), 6.99(brs, 2H), 7.50(d, 2H, J=8.0Hz), 7.87(d, 2H, J=8.0Hz), 7.78(d, 2H, J=9.0Hz), 7.96(s, 1H)	DMSO-d6, 300
2-31		>240	1.61(s, 6H), 1.89-2.13(m, 4H), 2.28-2.34(m, 2H), 2.55-2.62(m, 2H), 3.09-3.17(m, 1H), 6.97(brs, 2H), 7.39(d, 2H, J=9.0Hz), 7.68(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300

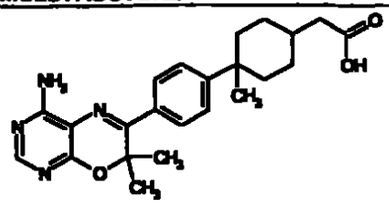
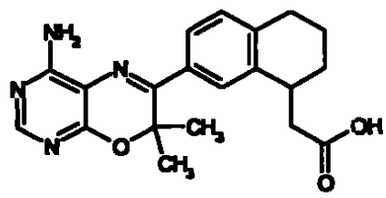
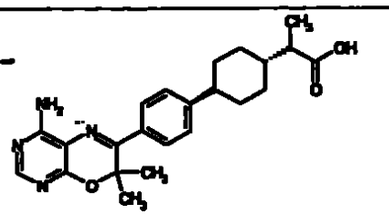
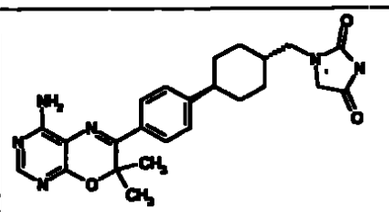
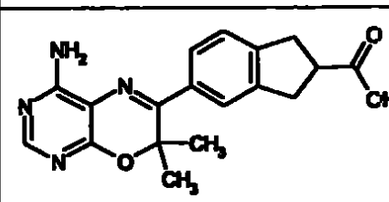
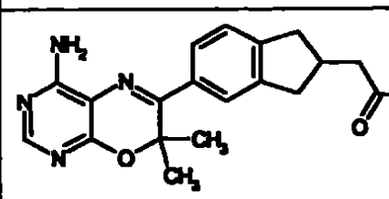
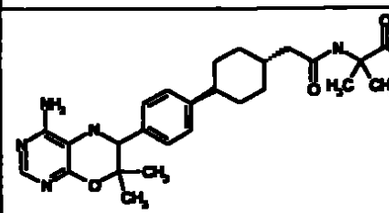
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-32		174 - 175	1.26-1.58(m, 7H), 1.61(s, 6H), 1.70-1.76(m, 2H), 1.92-1.98(m, 2H), 6.86(brs, 2H), 6.97(d, 2H, J=8.0Hz), 7.68(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400
2-33		185 - 186	0.91(t, 3H, J=8.0Hz), 1.57-1.66(m, 2H), 1.60(s, 6H), 2.61(t, 2H, J=8.0Hz), 6.89(br, 2H), 7.27(d, 2H, J=8.0Hz), 7.63(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 400MHz
2-34		220 - 220	1.33(s, 9H), 1.67(s, 6H), 7.49(d, 2H, J=8.0Hz), 7.58(br, 2H), 7.70(d, 2H, J=8.0Hz), 8.15(s, 1H)	DMSO-d6, 400MHz
2-35		135 - 136	1.21(t, 3H, J=7.0Hz), 1.60(s, 6H), 2.66(q, 2H, J=7.0Hz), 6.90(br, 2H), 7.29(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 400MHz
2-36		175 - 179	1.23(d, 6H, J=8.0Hz), 1.61(s, 6H), 2.91-2.98(m, 1H), 6.89(br, 2H), 7.32(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 400MHz
2-37		157 - 160	0.91(t, 3H, J=8.0Hz), 1.27-1.36(m, 2H), 1.54-1.61(m, 2H), 1.60(s, 6H), 2.63(t, 2H, J=8.0Hz), 6.90(br, 2H), 7.27(d, 2H, J=8.0Hz), 7.63(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 400MHz
2-38		189 - 190	1.35(t, 3H, J=8.0Hz), 1.61(s, 6H), 4.10(q, 2H, J=6.7Hz), 6.87(brs, 2H), 6.97(d, 2H, J=8.0Hz), 7.70(d, 2H, J=12.0Hz), 7.93(s, 1H)	DMSO-d6, 400

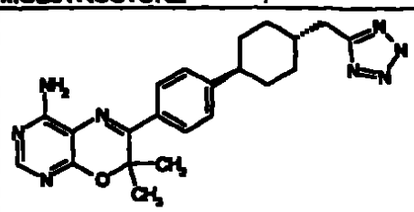
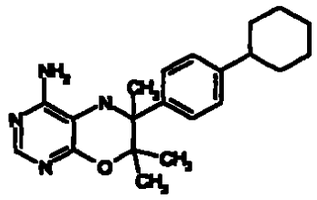
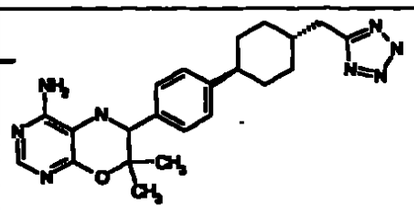
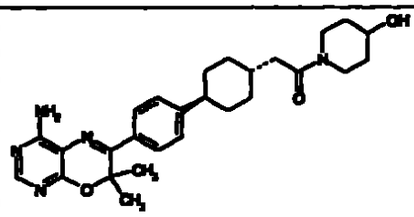
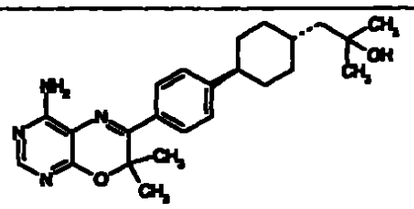
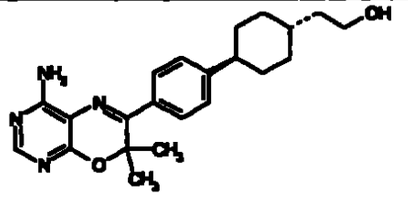
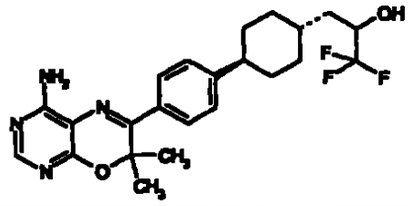
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-39		207 - 208	1.21(t, 3H, J=7.5Hz), 1.49-1.69(m, 6H), 1.93-2.08(m, 3H), 2.33-2.45(m, 2H), 2.84-2.94(m, 1H), 3.85-3.90(m, 1H), 4.09(q, 2H, J=7.0Hz), 5.72(s, 1H), 6.97(brs, 2H), 7.33(d, 2H, J=9.0Hz), 7.65(d, 2H, J=6.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-40		>250	1.46-1.63(m, 6H), 1.97-2.04(m, 3H), 2.32-2.38(m, 2H), 2.84-2.94(m, 1H), 3.85-3.90(m, 1H), 5.84(s, 1H), 6.90(brs, 2H), 7.32(d, 2H, J=8.0Hz), 7.84(d, 2H, J=8.0Hz), 7.94(s, 1H), 11.80(brs, 1H)	DMSO-d6, 400
2-41		201 - 209	0.93(d, 3H, J=6.5Hz), 1.03-1.13(m, 2H), 1.39-1.57(m, 3H), 1.62(s, 6H), 1.76-1.87(m, 4H), 2.49-2.58(m, 1H), 6.91(br, 2H), 7.31(d, 2H, J=8.4Hz), 7.78(d, 2H, J=8.4Hz), 7.98(s, 1H)	DMSO-d6, 400MHz
2-42		226 - 227	1.60(s, 6H), 1.64-1.74(m, 2H), 1.89-2.16(m, 6H), 2.75-2.81(m, 1H), 6.90(brs, 2H), 7.33(d, 2H, J=8.0Hz), 7.66(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 400
2-43		246 - 248	1.23-1.35(m, 2H), 1.43-1.56(m, 2H), 1.60(s, 6H), 1.75-1.81(m, 2H), 1.90-1.96(m, 2H), 2.46-2.54(m, 1H), 4.60(d, 1H, J=6.0Hz), 6.97(brs, 2H), 7.30(d, 2H, J=9.0Hz), 7.64(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-44			1.40-1.60(m, 2H), 1.60(s, 6H), 1.90-2.00(m, 3H), 2.25-2.40(m, 2H), 2.85(s, 3H), 3.00(s, 3H), 3.13(m, 1H), 5.89(s, 1H), 6.90(brs, 2H), 7.31(d, 2H, J=8.3 Hz), 7.64(d, 2H, J=8.3 Hz), 7.94(s, 1H).	DMSO-d6, 400MHz
2-45		142 - 144	1.40-1.60(m, 2H), 1.60(s, 6H), 1.90-2.00(m, 3H), 2.25-2.40(m, 2H), 2.80(m, 1H), 4.13(m, 1H), 4.30(d, 2H, J=6.0 Hz), 5.89(s, 1H), 6.90(brs, 2H), 7.20-7.33(m, 6H), 7.64(d, 2H, J=8.3 Hz), 7.94(s, 1H), 8.30(brt, 1H, J=6.0Hz).	DMSO-d6, 400MHz

New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-46			1.45-1.57(m, 2H), 1.80(s, 6H), 1.84-2.00(m, 3H), 2.23-2.36(m, 2H), 2.75-2.89(m, 1H), 5.57(s, 1H), 6.77(brs, 1H), 6.97(brs, 2H), 7.26(brs, 1H), 7.32(d, 2H, J=9.0Hz), 7.88(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-47		229 - 230	1.03(t, 3H, J=7.5Hz), 1.45-1.58(m, 3H), 1.80(s, 6H), 1.81-2.32(m, 5H), 2.73-2.89(m, 1H), 3.05-3.14(m, 2H), 5.65(s, 1H), 6.97(brs, 2H), 7.32(d, 2H, J=9.0Hz), 7.85(d, 2H, J=9.0Hz), 7.80-7.84(m, 1H), 7.95(s, 1H)	DMSO-d6, 300
2-48			1.45-1.58(m, 3H), 1.80(s, 6H), 1.84-2.02(m, 3H), 2.22-2.36(m, 2H), 2.80-2.89(m, 1H), 3.12-3.19(m, 2H), 3.38-3.43(m, 2H), 4.07-4.14(m, 0.5H), 4.65-4.70(m, 0.5H), 5.68(s, 1H), 6.97(brs, 2H), 7.32(d, 2H, J=9.0Hz), 7.85(d, 2H, J=9.0Hz), 7.84(t, 1H, J=6.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-49			0.88-1.09(m, 2H), 1.27-1.59(m, 3H), 1.88(s, 6H), 1.78-1.88(m, 4H), 2.33-2.47(m, 1H), 2.63-2.73(m, 2H), 2.77-2.88(m, 2H), 3.08(t, 2H, J=7.0Hz), 4.88(s, 2H), 6.99(t, 1H, J=5.8Hz), 7.11(d, 2H, J=8.3Hz), 7.28(s, 2H), 7.43(d, 2H, J=8.3Hz)	DMSO-d6, 300MHz
2-50			1.41-1.80(m, 2H), 1.80(s, 6H), 1.91-2.03(m, 3H), 2.16-2.42(m, 9H), 2.79-2.88(m, 1H), 2.95-3.05(m, 1H), 3.42-3.49(m, 1H), 3.49(br, 3H), 5.87(s, 1H), 6.88(br, 2H), 7.31(d, 2H, J=8.6Hz), 7.84(d, 2H, J=8.6Hz), 7.94(s, 1H)	DMSO-d6, 400MHz
2-51			1.43-1.59(m, 2H), 1.80(s, 6H), 1.87-2.01(m, 3H), 2.18(s, 6H), 2.28-2.34(m, 4H), 2.79-2.88(m, 1H), 3.18(q, 2H, J=6.4Hz), 4.05-4.10(m, 1H), 5.67(s, 1H), 6.89(br, 2H), 7.31(d, 2H, J=8.1Hz), 7.84(d, 2H, J=8.1Hz), 7.89(t, 1H, J=6.4Hz), 7.94(s, 1H)	DMSO-d6, 400MHz
2-52		212 - 215	1.41(s, 9H), 1.47-1.63(m, 2H), 1.80(s, 6H), 1.88-2.03(m, 3H), 2.28-2.34(m, 2H), 2.82-2.89(m, 1H), 3.74(d, 2H, J=6.1Hz), 3.98-4.08(m, 1H), 5.72(s, 1H), 6.90(br, 2H), 7.31(d, 2H, J=8.1Hz), 7.84(d, 2H, J=8.1Hz), 7.94(s, 1H), 8.11(t, 1H, J=6.1Hz)	DMSO-d6, 400MHz

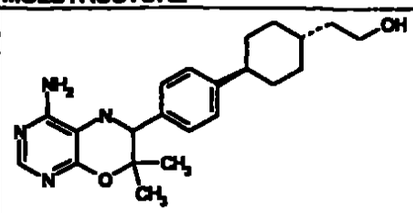
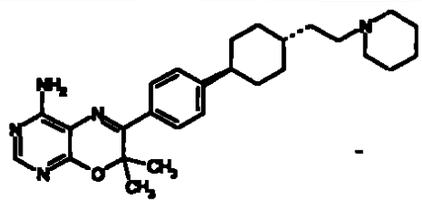
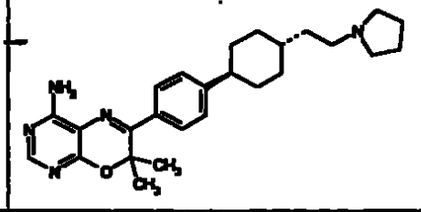
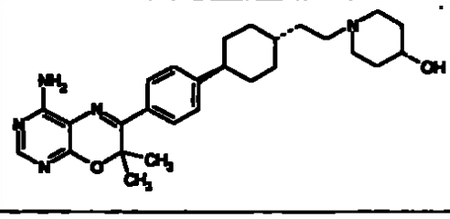
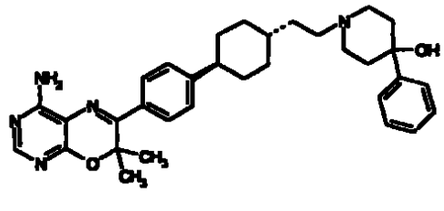
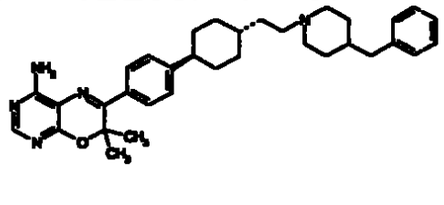
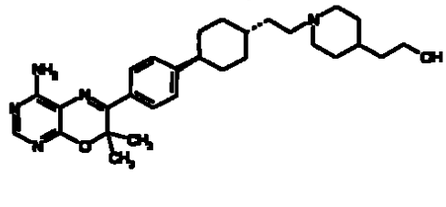
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-53		>270	1.65(s, 6H), 3.64(s, 2H), 7.04(brs, 2H), 7.39(d, 2H, J=9.0Hz), 7.69(d, 2H, J=9.0Hz), 7.75(d, 2H, J=9.0Hz), 7.84(d, 2H, J=9.0Hz), 12.32(brs, 1H)	DMSO-d6, 300
2-54		267(dec.)	1.12(s, 3H), 1.28(s, 3H), 3.62(s, 2H), 4.22(brs, 1H), 5.35(brs, 1H), 6.27(brs, 2H), 7.36(d, 2H, J=9.0Hz), 7.54(d, 2H, J=9.0Hz), 7.85(d, 2H, J=9.0Hz), 7.84(s, 1H), 7.70(d, 2H, J=9.0Hz)	DMSO-d6, 300
2-55		>250	1.49(s, 6H), 1.60(s, 6H), 6.98(brs, 2H), 7.40(d, 2H, J=8.4 Hz), 7.88(d, 2H, J=8.4 Hz), 7.95(s, 1H), 12.4(brs, 1H).	DMSO-d6, 300MHz
2-56				
2-67				
2-58		251 - 252	1.01-1.13(m, 2H), 1.39-1.53(m, 3H), 1.60(s, 6H), 1.82-1.91(m, 4H), 2.53-2.57(m, 1H), 2.83(t, 2H, J=6.0Hz), 2.88(s, 3H), 6.94(brs, 2H), 7.01(t, 1H, J=6.0Hz), 7.32(d, 2H, J=9.0Hz), 7.65(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-59		>250	1.04-1.12(m, 2H), 1.43-1.60(m, 3H), 1.60(s, 6H), 1.77-1.83(m, 4H), 2.38(d, 2H, J=6.9 Hz), 2.49(m, 1H), 5.24(s, 1H), 6.88(brs, 2H), 7.29(d, 2H, J=8.3 Hz), 7.62(d, 2H, J=8.3 Hz), 7.94(s, 1H), 9.20(brs, 1H), 11.20(brs, 1H).	DMSO-d6, 400MHz

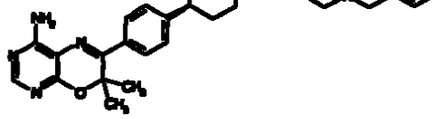
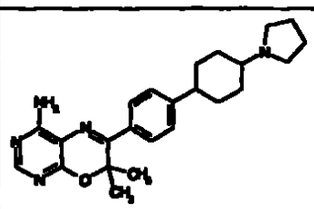
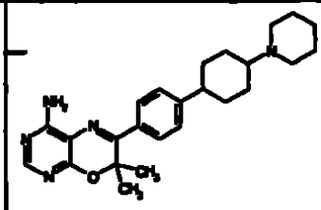
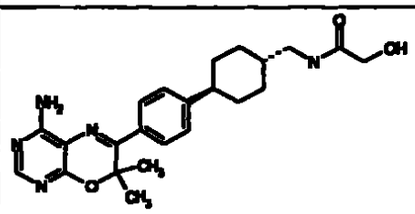
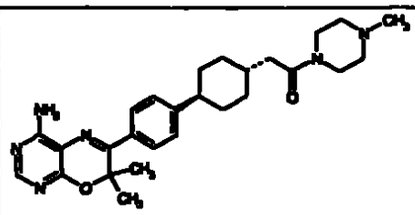
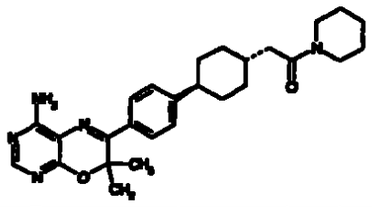
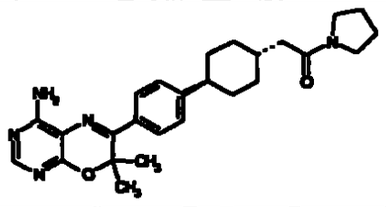
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-60		173 - 175	a mixture of keto- and enol-form; 1.04-1.12(m, 2H), 1.43-1.60(m, 2H), 1.60(s, 6H), 1.70(m,1H), 1.81-1.85(m, 4H), 2.33(d, 1H, J=8.9 Hz) and 2.37(d, 1H, J=8.9 Hz), 2.50(m, 1H), 3.85(s, 1H) and 5.00(s, 0.5H), 6.88(brs, 2H), 7.29(d, 2H, J=8.3 Hz), 7.84(d, 2H, J=8.3 Hz), 7.95(s, 1H), 12.40(brs, 0.5H).	DMSO-d6, 400MHz
2-61		159 - 162	0.97-1.13(m, 2H), 1.35-1.52(m, 3H), 1.60(s, 6H), 1.76-1.87(m, 4H), 2.46-2.58(m, 1H), 2.91(t, 2H, J=6.0Hz), 5.02(s, 2H), 6.94(br, 2H), 7.23-7.40(m, 8H), 7.84(d, 2H, J=7.7Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-62		>230	1.25-1.40(m, 2H), 1.45-1.55(m, 2H), 1.60(s, 6H), 1.83(brd, 2H, J=12.6 Hz), 2.11(brd, 2H, J=9.6 Hz), 2.55(m, 1H), 3.35(m, 1H), 4.05(s, 2H), 6.88(brs, 2H), 7.29(d, 2H, J=8.3 Hz), 7.83(d, 2H, J=8.3 Hz), 7.94(s, 1H), 12.30(brs, 1H).	DMSO-d6, 400MHz
2-63			0.99-1.08(m, 2H), 1.24-1.34(m, 1H), 1.39-1.51(m, 2H), 1.60(s, 6H), 1.76-1.92(m, 4H), 2.44(d, 2H, J=6.6Hz), 2.47-2.58(m, 1H), 6.89(br, 2H), 7.30(d, 2H, J=8.2Hz), 7.83(d, 2H, J=8.2Hz), 7.95(s, 1H)	DMSO-d6, 400MHz
2-64		>230	1.04-1.20(m, 2H), 1.43-1.50(m, 3H), 1.60(s, 6H), 1.75-1.86(m, 5H), 2.02(m, 1H), 2.51(m, 1H), 4.80(m, 1H), 6.88(brs, 2H), 7.30(d, 2H, J=8.3 Hz), 7.83(d, 2H, J=8.3 Hz), 7.94(s, 1H), 12.02(brs, 1H).	DMSO-d6, 400MHz
2-65		243 - 244	1.05-1.14(m, 2H), 1.33(s, 6H), 1.38-1.51(m, 2H), 1.60(s, 6H), 1.76-1.85(m, 5H), 2.00(d, 2H, J=6.0Hz), 2.54-2.55(m, 1H), 6.94(brs, 2H), 7.31(d, 2H, J=9.0Hz), 7.84(d, 2H, J=9.0Hz), 7.95(s, 1H), 7.98(s, 1H)	DMSO-d6, 300MHz
2-66		176-177	1.59(s, 6H), 1.72-1.77(m, 4H), 2.72-2.82(m, 4H), 6.92(br, 2H), 7.11(d, 1H, J=7.7Hz), 7.40(d, 1H, J=7.7Hz), 7.39(s, 1H), 7.95(s, 1H)	DMSO-d6, 300MHz

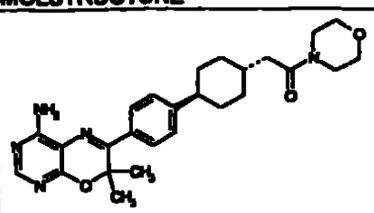
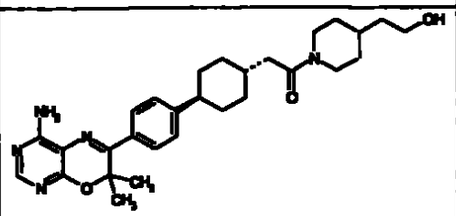
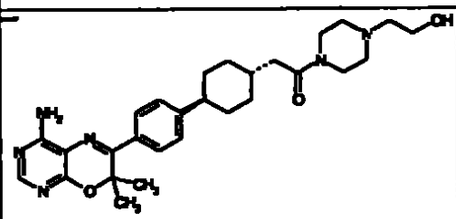
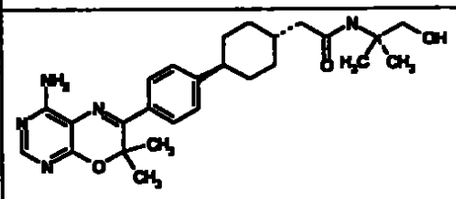
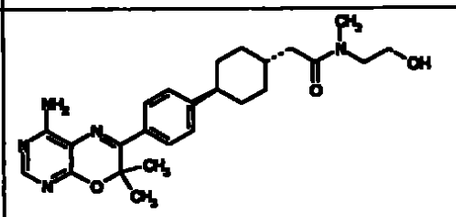
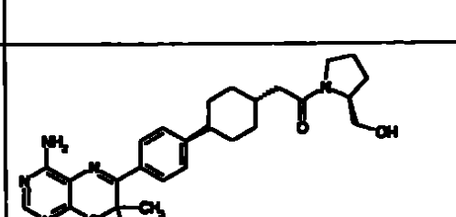
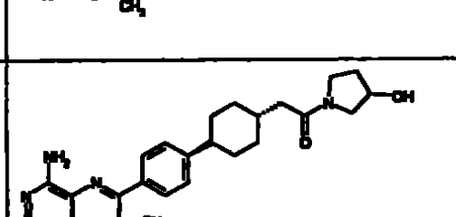
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-67		>250	0.80-0.96(m, 2H), 1.11(s, 3H), 1.41-1.65(m, 4H), 1.62(s, 6H), 1.65-1.79(m, 1H), 1.96(d, 2H, J=7.0Hz), 2.31-2.41(m, 2H), 6.95(br, 2H), 7.44(d, 2H, J=8.4Hz), 7.70(d, 2H, J=8.4Hz), 7.95(s, 1H), 11.86(bra, 1H)	DMSO-d6, 300MHz
2-68		>250	1.53-1.90(m, 5H), 1.59(s, 6H), 2.40-2.52(m, 2H), 2.68-2.82(m, 3H), 6.93(br, 2H), 7.13(d, 1H, J=7.7Hz), 7.44(d, 1H, J=7.7Hz), 7.50(s, 1H), 7.95(s, 1H), 12.15(bra, 1H)	DMSO-d6, 300MHz
2-69		>250	1.06(d, 3H, J=7.1Hz), 1.11-1.28(m, 2H), 1.43-1.52(m, 2H), 1.55-1.65(m, 1H), 1.61(s, 6H), 1.71-1.91(m, 4H), 2.15-2.23(m, 1H), 2.49-2.58(m, 1H), 6.92(br, 2H), 7.31(d, 2H, J=8.1Hz), 7.64(d, 2H, J=8.1Hz), 7.95(s, 1H), 11.97(bra, 1H)	DMSO-d6, 400MHz
2-70		212 - 214	1.04-1.20(m, 2H), 1.43-1.50(m, 2H), 1.60(s, 6H), 1.61(m, 1H), 1.75-1.88(m, 4H), 2.51(m, 1H), 3.11(d, 2H, J=7.2 Hz), 3.95(s, 2H), 6.88(bra, 2H), 7.29(d, 2H, J=8.3 Hz), 7.64(d, 2H, J=8.3 Hz), 7.94(s, 1H), 10.68(bra, 1H).	DMSO-d6, 400MHz
2-71		>250	1.59(s, 6H), 3.10-3.21(m, 4H), 3.28-3.34(m, 1H), 6.94(br, 2H), 7.28(d, 1H, J=7.7Hz), 7.48(d, 1H, J=7.7Hz), 7.55(s, 1H), 12.29(bra, 1H)	DMSO-d6, 300MHz
2-72		>250	1.59(s, 6H), 2.42(d, 2H, J=7.3Hz), 2.57-2.80(m, 3H), 3.04-3.15(m, 2H), 6.92(br, 2H), 7.28(d, 1H, J=8.1Hz), 7.48(d, 1H, J=8.1Hz), 7.53(s, 1H), 7.95(s, 1H), 12.06(bra, 1H)	DMSO-d6, 300MHz
2-73		>250	1.03-1.13(m, 2H), 1.06(s, 3H), 1.22(s, 3H), 1.32(s, 6H), 1.36-1.48(m, 2H), 1.67-1.86(m, 5H), 1.99(d, 2H, J=6.6Hz), 2.42-2.50(m, 1H), 4.11(s, 1H), 5.25(s, 1H), 6.20(br, 2H), 7.24(d, 2H, J=8.1Hz), 7.35(d, 2H, J=8.1Hz), 7.81(s, 1H), 7.94(s, 1H), 11.93(bra, 1H)	DMSO-d6, 400MHz

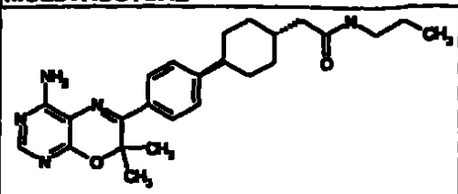
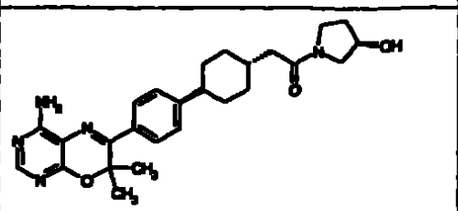
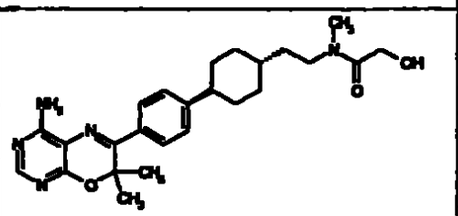
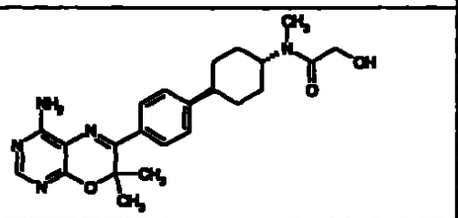
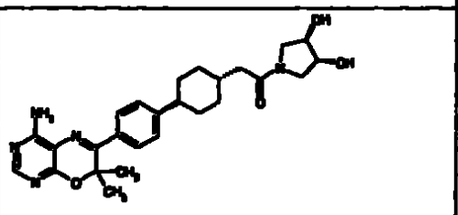
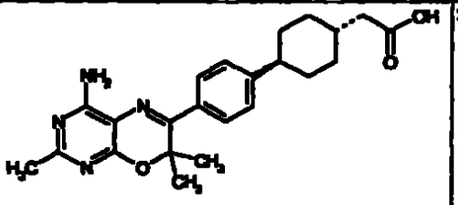
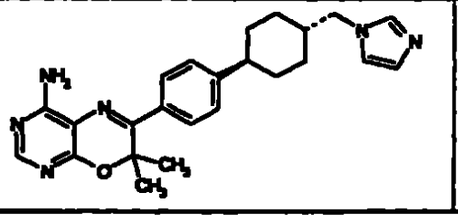
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-74		>250	1.11-1.27(m, 2H), 1.36-1.54(m, 2H), 1.80(s, 6H), 1.68-1.87(m, 5H), 2.50-2.61(m, 1H), 2.83(d, 2H, J=7.0Hz), 6.93(br, 2H), 7.30(d, 2H, J=8.4Hz), 7.84(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-75		244 - 245	1.03(s, 3H), 1.26(s, 3H), 1.33-1.43(m, 4H), 1.46(s, 3H), 1.68-1.80(m, 6H), 2.52-2.55(m, 1H), 5.16(s, 1H), 6.23(bra, 2H), 7.23(d, 2H, J=8.0Hz), 7.53(d, 2H, J=9.0Hz), 7.81(s, 1H)	DMSO-d6, 300MHz
2-76		>250	1.11-1.27(m, 2H), 1.36-1.51(m, 2H), 1.68-1.87(m, 5H), 2.41-2.52(m, 1H), 2.83(d, 2H, J=6.6Hz), 4.11(s, 1H), 5.25(s, 1H), 6.20(br, 2H), 7.23(d, 2H, J=8.1Hz), 7.35(d, 2H, J=8.1Hz), 7.81(s, 1H), 15.98(bra, 1H)	DMSO-d6, 400MHz
2-77		137 - 139	1.04-1.34(m, 4H), 1.43-1.50(m, 2H), 1.80(s, 6H), 1.63-1.88(m, 7H), 2.23(d, 2H, J=7.2 Hz), 2.51(m, 1H), 3.00(m, 1H), 3.15(m, 1H), 3.68-3.78(m, 2H), 3.94(m, 1H), 4.65(bra, 1H), 6.88(bra, 2H), 7.30(d, 2H, J=8.3 Hz), 7.83(d, 2H, J=8.3 Hz), 7.94(s, 1H).	DMSO-d6, 400MHz
2-78		185 - 187	1.04-1.20(m, 2H), 1.12(s, 6H), 1.31(d, 2H, J=5.4 Hz), 1.43-1.50(m, 3H), 1.80(s, 6H), 1.75-1.95(m, 4H), 2.51(m, 1H), 4.01(s, 1H), 6.86(bra, 2H), 7.29(d, 2H, J=8.3 Hz), 7.83(d, 2H, J=8.3 Hz), 7.94(s, 1H).	DMSO-d6, 400MHz
2-79		207 - 208	1.00-1.14(m, 2H), 1.34-1.51(m, 5H), 1.80-1.91(m, 4H), 2.53-2.57(m, 1H), 3.43-3.48(m, 2H), 4.27(bra, 1H), 6.92(bra, 2H), 7.30(d, 2H, J=9.0Hz), 7.84(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-80		271 - 272	0.98-1.24(m, 2H), 1.33-1.84(m, 10H), 1.76-1.98(m, 5H), 2.52-2.58(m, 1H), 3.98-4.03(m, 1H), 6.04(bra, 1H), 6.91(bra, 2H), 7.31(d, 2H, J=8.0Hz), 7.84(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 400

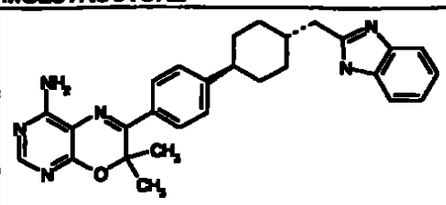
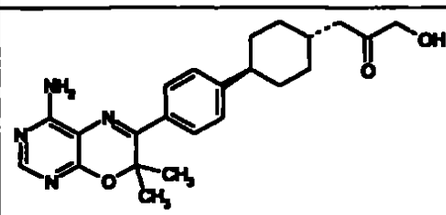
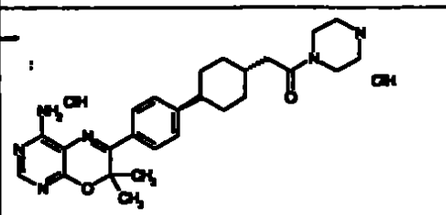
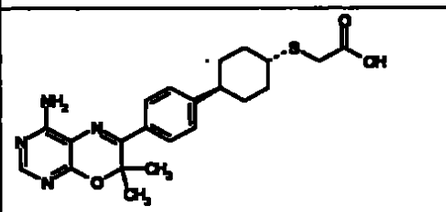
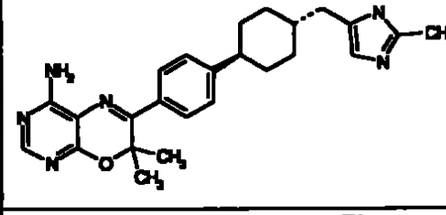
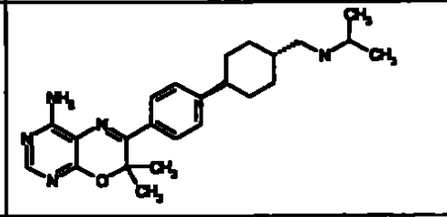
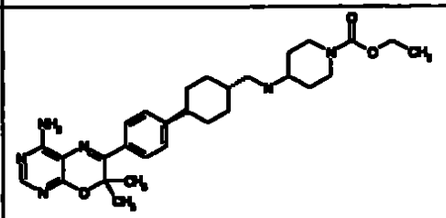
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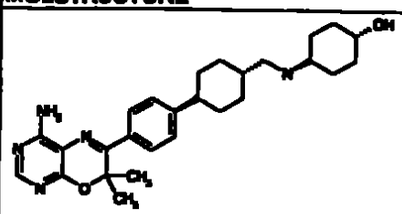
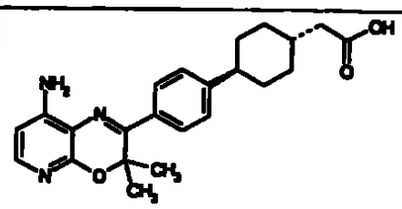
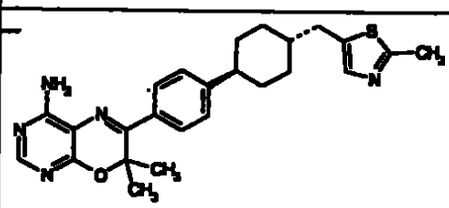
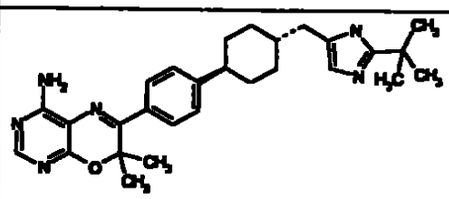
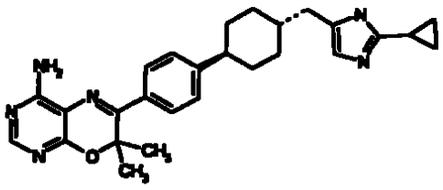
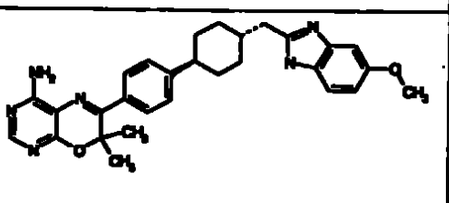
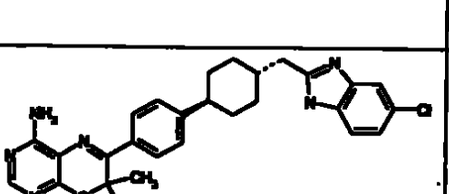
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-81			1.00-1.11(m, 5H), 1.22(s, 3H), 1.33-1.49(m, 5H), 1.75-1.85(m, 4H), 2.41-2.49(m, 1H), 3.43-3.49(m, 2H), 4.11(bra, 1H), 4.28-4.33(m, 1H), 5.28(bra, 1H), 6.22(bra, 2H), 7.24(d, 2H, J=9.0Hz), 7.38(d, 2H, J=9.0Hz), 7.82(s, 1H)	DMSO-d6, 300
2-82		209 - 210	1.08-1.17(m, 2H), 1.32-1.52(m, 6H), 1.68-1.90(m, 11H), 1.61(s, 6H), 2.54-2.63(m, 1H), 2.77-2.89(m, 2H), 2.99-3.10(m, 2H), 7.03(bra, 2H), 7.31(d, 2H, J=9.0Hz), 7.85(d, 2H, J=9.0Hz), 7.98(s, 1H)	DMSO-d6, 300MHz
2-83		142 - 143	1.04-1.16(m, 2H), 1.37-1.54(m, 6H), 1.80(bra, 6H), 1.79-2.02(m, 9H), 2.54-2.60(m, 1H), 2.91-3.03(m, 2H), 3.07-3.22(m, 2H), 7.03(bra, 2H), 7.31(d, 2H, J=9.0Hz), 7.88(d, 2H, J=9.0Hz), 7.98(bra, 1H)	DMSO-d6, 300MHz
2-84		217 - 218	1.02-1.14(m, 2H), 1.33-1.49(m, 10H), 1.80(s, 6H), 1.89-1.86(m, 9H), 2.54-2.58(m, 1H), 2.71-2.81(m, 2H), 3.42-3.52(m, 1H), 4.56(bra, 1H), 6.92(bra, 2H), , 7.30(d, 2H, J=9.0Hz), 7.84(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-85		115 - 116	1.04-1.16(m, 2H), 1.34-1.51(m, 6H), 1.58-1.66(m, 2H), 1.60(s, 6H), 1.80-1.98(m, 7H), 2.38-2.49(m, 2H), 2.51-2.60(m, 1H), 2.68-2.80(m, 2H), 4.80(bra, 1H), 6.92(bra, 2H), 7.18-7.34(m, 5H), 7.49(d, 2H, J=9.0Hz), 7.85(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-86		190 - 191	1.01-1.23(m, 4H), 1.30-1.57(m, 7H), 1.60(s, 6H), 1.74-1.86(m, 7H), 2.25-2.31(m, 2H), 2.53-2.57(m, 1H), 2.80-2.86(m, 2H), 3.30(s, 2H), 6.91(bra, 2H), 7.14-7.30(m, 7H), 7.84(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-87		221 - 222	1.02-1.14(m, 4H), 1.31-1.64(m, 9H), 1.60(s, 6H), 1.78-1.87(m, 7H), 2.27-2.37(m, 2H), 2.54-2.57(m, 1H), 2.80-2.90(m, 2H), 3.40-3.46(m, 2H), 4.29(t, 1H, J=4.5Hz), 6.92(bra, 2H), 7.30(d, 2H, J=9.0Hz), 7.84(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz

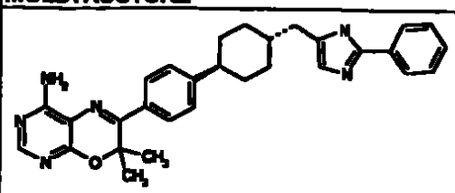
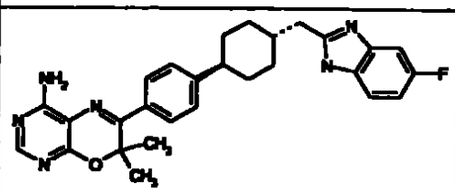
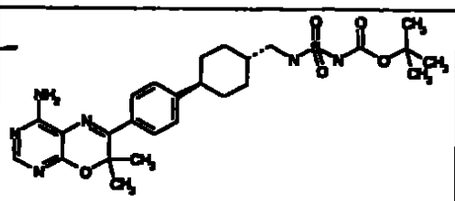
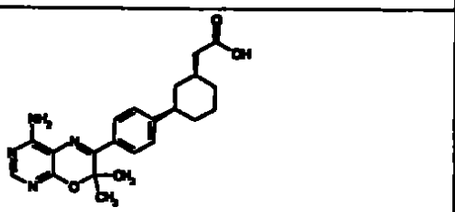
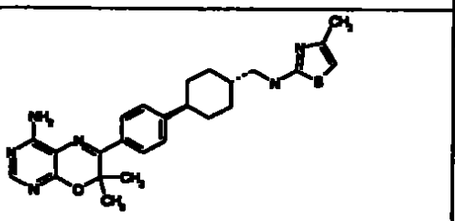
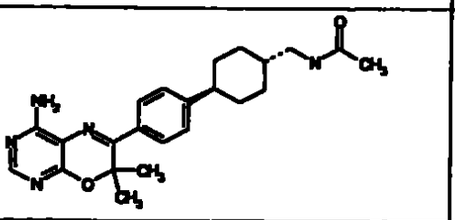
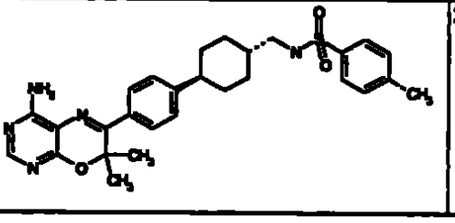
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-88		175 - 176	1.05-1.13(m, 2H), 1.34-1.50(m, 6H), 1.60(s, 6H), 1.79-1.85(m, 5H), 2.31-2.45(m, 8H), 2.53-2.57(m, 1H), 3.46(s, 2H), 6.92(brs, 2H), 7.24-7.35(m, 7H), 7.84(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-89			1.47-1.67(m, 6H), 1.70(s, 6H), 1.74-1.86(m, 3H), 1.88-2.07(m, 4H), 2.17-2.27(m, 1H), 2.44-2.61(m, 3H), 2.84-2.74(m, 1H), 5.40(br, 2H), 7.34(br, 2H), 7.55(br, 2H), 8.14(s, 1H)	CDCl3, 400MHz
2-90			1.34-1.85(m, 10H), 1.61(s, 6H), 1.81-1.99(m, 5H), 2.14-2.27(m, 1H), 2.31-2.45(m, 3H), 2.68-2.83(m, 1H), 6.90(br, 2H), 7.31(br, 2H), 7.85(br, 2H), 7.95(s, 1H)	DMSO-d6, 400MHz
2-91			1.04-1.13(m, 2H), 1.38-1.58(m, 3H), 1.60(s, 6H), 1.75-1.95(m, 3H), 2.51(m, 1H), 3.01(brt, 2H, J=6.4 Hz), 3.80(d, 2H, J=5.6 Hz), 5.41(brt, 1H, J=5.6 Hz), 6.90(brs, 2H), 7.28(d, 2H, J=8.3 Hz), 7.82(d, 2H, J=8.3 Hz), 7.69(brt, 1H, J=6.4 Hz), 7.93(s, 1H).	DMSO-d6, 400MHz
2-92		113 - 115	1.04-1.17(m, 2H), 1.43-1.50(m, 2H), 1.60(s, 6H), 1.80-1.84(m, 6H), 2.19(s, 3H), 2.23-2.31(m, 6H), 2.51(m, 1H), 3.43-3.48(m, 4H), 6.91(brs, 2H), 7.30(d, 2H, J=8.3 Hz), 7.83(d, 2H, J=8.3 Hz), 7.95(s, 1H).	DMSO-d6, 300MHz
2-93		146 - 147	1.03-1.20(m, 2H), 1.37-1.88(m, 19H), 2.22(d, 2H, J=6.0Hz), 2.53-2.58(m, 1H), 3.39-3.46(m, 4H), 6.92(brs, 2H), 7.31(d, 2H, J=9.0Hz), 7.84(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-94		232 - 233	1.06-1.19(m, 2H), 1.41-1.83(m, 8H), 1.71-1.91(m, 8H), 2.16(d, 2H, J=6.0Hz), 2.51-2.59(m, 1H), 3.28-3.31(m, 2H), 3.41(t, 2H, J=6.0Hz), 6.92(brs, 2H), 7.31(d, 2H, J=9.0Hz), 7.84(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300

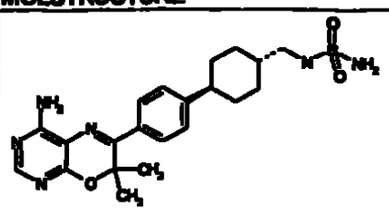
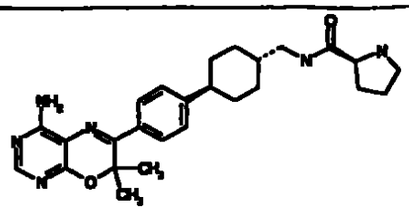
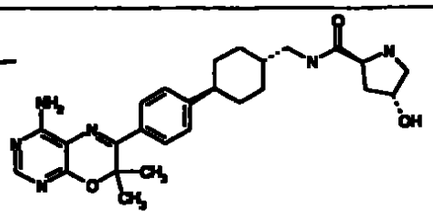
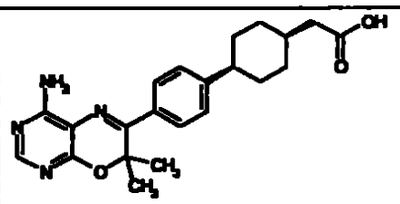
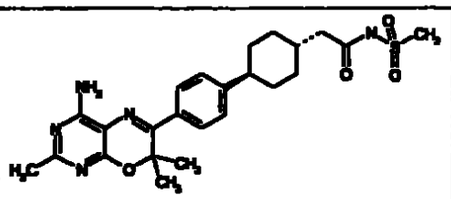
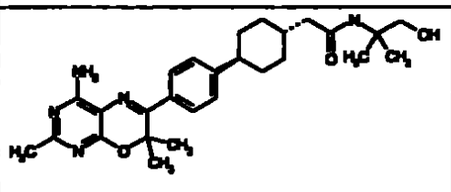
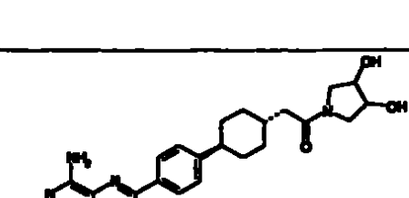
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-95		199 - 200	1.06-1.21(m, 2H), 1.41-1.58(m, 2H), 1.60(s, 6H), 1.74-1.87(m, 4H), 2.25(d, 2H, J=9.0Hz), 3.41-3.59(m, 10H), 6.93(bra, 2H), 7.31(d, 2H, J=9.0Hz), 7.84(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-96		112 - 113	0.89-1.18(m, 4H), 1.32-1.55(m, 4H), 1.60(s, 6H), 1.67-1.83(m, 7H), 2.22(d, 2H, J=6.0Hz), 2.52-2.57(m, 1H), 2.92-3.02(m, 2H), 3.41-3.47(m, 2H), 3.84-3.92(m, 2H), 4.33-4.42(m, 2H), 6.93(bra, 2H), 7.31(d, 2H, J=9.0Hz), 7.84(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-97		225 - 226	1.06-1.18(m, 2H), 1.41-1.53(m, 2H), 1.60(s, 6H), 1.74-1.83(m, 5H), 2.23(d, 2H, J=6.0Hz), 2.33-2.42(m, 6H), 2.53-2.58(m, 1H), 3.43-3.54(m, 6H), 4.41(t, 1H, J=6.0Hz), 6.93(bra, 2H), 7.31(d, 2H, J=9.0Hz), 7.84(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-98		131 - 133	1.04-1.13(m, 2H), 1.18(s, 6H), 1.38-1.58(m, 2H), 1.59(s, 6H), 1.65-1.85(m, 5H), 1.97(d, 2H, J=6.8 Hz), 2.51(m, 1H), 3.38(d, 2H, J=5.9 Hz), 4.89(t, 1H, J=5.9 Hz), 6.92(bra, 2H), 7.24(s, 1H), 7.27(d, 2H, J=8.3 Hz), 7.81(d, 2H, J=8.3 Hz), 7.92(s, 1H).	DMSO-d6, 400MHz
2-99		113 - 115	a mixture of 2 conformers; 1.04-1.13(m, 2H), 1.38-1.58(m, 2H), 1.60(s, 6H), 1.65-1.85(m, 5H), 2.20-2.28(m, 2H), 2.51(m, 1H), 2.82 and 3.01(s, 3H), 3.30-3.51(m, 4H), 4.80 and 4.77(brt, 1H, J=5.6 Hz), 6.92(bra, 2H), 7.29(d, 2H, J=8.3 Hz), 7.62(d, 2H, J=8.3 Hz), 7.93(s, 1H).	DMSO-d6, 400MHz
2-100		184 - 185	1.03-1.21(m, 2H), 1.39-1.55(m, 2H), 1.62(s, 6H), 1.71-1.95(m, 6H), 2.13-2.36(m, 2H), 2.43-2.59(m, 1H), 3.22-3.52(m, 4H), 3.85-4.02(m, 1H), 4.87-4.92(m, 1H), 6.91(br, 2H), 7.31(d, 2H, J=8.4Hz), 7.84(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-101		237 - 239	1.02-1.20(m, 2H), 1.37-1.57(m, 2H), 1.60(s, 6H), 1.69-1.95(m, 7H), 2.09-2.20(m, 2H), 2.44-2.59(m, 1H), 3.33-3.54(m, 2H), 4.20-4.38(m, 2H), 4.80-5.00(m, 1H), 6.92(br, 2H), 7.31(d, 2H, J=8.4Hz), 7.84(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz

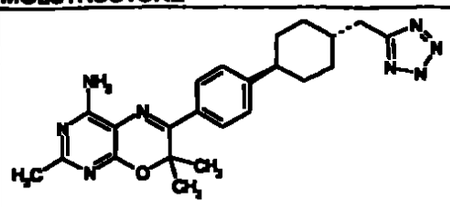
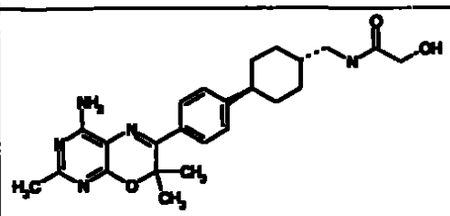
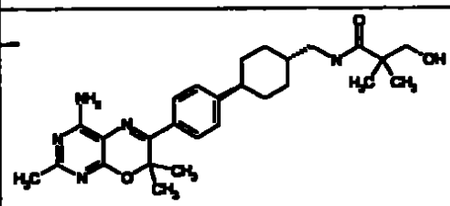
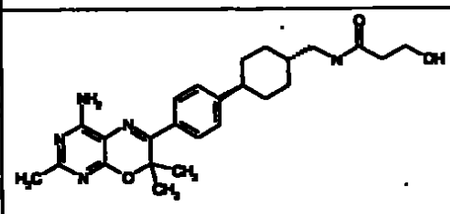
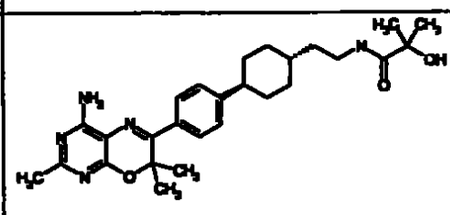
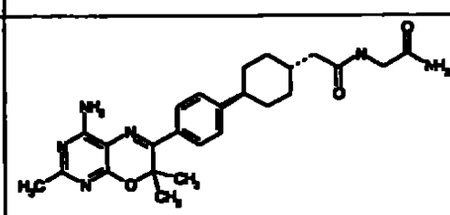
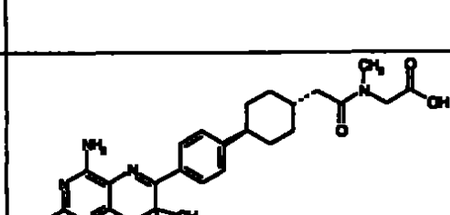
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-102		214 - 215	0.84(t, 3H, J=7.3Hz), 1.02-1.19(m, 2H), 1.34-1.53(m, 4H), 1.60(s, 6H), 1.69-1.86(m, 5H), 1.99(d, 2H, J=6.6Hz), 2.48-2.57(m, 1H), 3.00(q, 2H, J=6.6Hz), 6.93(br, 2H), 7.30(d, 2H, J=8.4Hz), 7.64(d, 2H, J=8.4Hz), 7.74(t, 1H, J=6.6Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-103		231 - 232	1.02-1.22(m, 2H), 1.39-1.57(m, 2H), 1.60(s, 6H), 1.69-1.97(m, 5H), 2.08-2.21(m, 2H), 2.47-2.59(m, 1H), 3.29-3.58(m, 4H), 4.15-4.41(m, 2H), 4.81-5.00(m, 1H), 6.89(br, 2H), 7.31(d, 2H, J=8.4Hz), 7.64(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-104		186 - 188	1.00-1.55(m, 7H), 1.60(s, 6H), 1.78-1.94(m, 4H), 2.46-2.61(m, 1H), 2.85(s, 3H), 4.05(s, 1.4H), 4.08(s, 0.6H), 6.92(br, 2H), 7.30(d, 2H, J=8.1Hz), 7.64(d, 2H, J=8.1Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-105		>250	1.52-1.92(m, 8H), 1.61(s, 6H), 2.49-2.65(m, 1H), 2.76(s, 1.8H), 2.79(s, 1.2H), 4.06(s, 0.6H), 4.16(s, 0.4H), 4.25-4.47(m, 1H), 6.93(br, 2H), 7.33(brd, 2H, J=8.2Hz), 7.65(d, 2H, J=8.2Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-106		250 - 252	1.03-1.22(m, 2H), 1.39-1.58(m, 2H), 1.60(s, 6H), 1.69-1.92(m, 5H), 2.12(d, 2H, J=6.6Hz), 2.45-2.58(m, 1H), 3.16-3.41(m, 3H), 3.55-3.60(m, 1H), 3.94-4.09(m, 2H), 4.84(br, 1H), 4.92(br, 1H), 6.93(br, 2H), 7.31(d, 2H, J=8.1Hz), 7.64(d, 2H, J=8.1Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-107		>250	1.07-1.18(m, 2H), 1.41-1.53(m, 2H), 1.59(s, 6H), 1.71-1.86(m, 5H), 2.15(d, 2H, J=4.0Hz), 2.24(s, 3H), 2.51-2.57(m, 1H), 6.84(brs, 2H), 7.28(d, 2H, J=8.0Hz), 7.81(d, 2H, J=8.0Hz), 12.04(brs, 1H)	DMSO-d6, 400MHz
2-108		202 - 203	1.06-1.16(m, 2H), 1.36-1.48(m, 2H), 1.59-1.84(m, 5H), 1.59(s, 6H), 2.51-2.56(m, 1H), 3.86(d, 2H, J=8.0Hz), 6.89-7.15(m, 1H), 6.91(brs, 2H), 7.27(d, 2H, J=8.0Hz), 7.62(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz

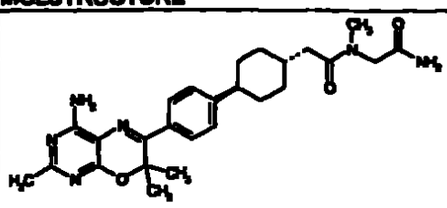
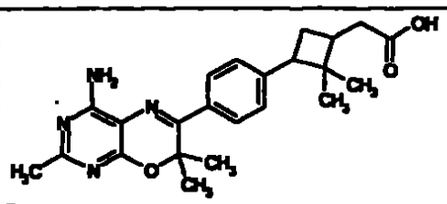
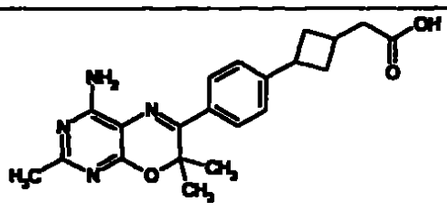
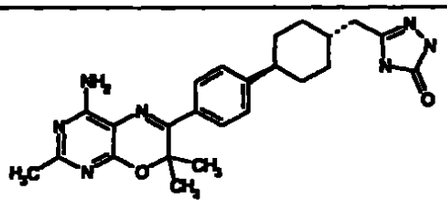
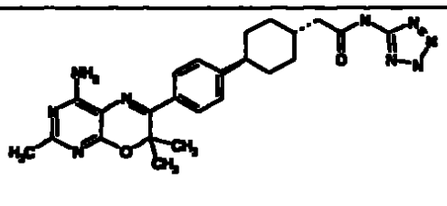
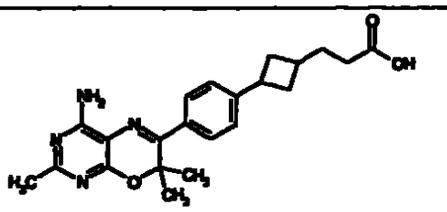
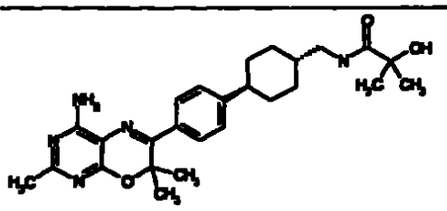
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-109		>230	1.15-1.35(m, 2H), 1.37-1.58(m, 3H), 1.60(s, 6H), 1.80-1.95(m, 5H), 2.51(m, 1H), 2.75(d, 2H, J=9.3 Hz), 6.91(brs, 2H), 7.03-7.22(m, 2H), 7.30(d, 2H, J=8.3 Hz), 7.39-7.57(m, 2H), 7.63(d, 2H, J=8.3 Hz), 7.95(s, 1H), 12.19(brs, 1H).	DMSO-d6, 400MHz
2-110		155 - 158	1.01-1.18(m, 2H), 1.38-1.59(m, 2H), 1.60(s, 6H), 1.72-1.86(m, 5H), 2.34(d, 2H, J=6.0Hz), 2.54-2.58(m, 1H), 4.05(d, 2H, J=6.0Hz), 5.04(t, 1H, J=6.0Hz), 6.91(brs, 2H), 7.31(d, 2H, J=9.0Hz), 7.64(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-111		>250	1.04-1.21(m, 2H), 1.38-1.58(m, 2H), 1.66(s, 6H), 1.70-1.89(m, 5H), 2.29(d, 2H, J=6.4Hz), 2.45-2.58(m, 1H), 2.96-3.13(m, 4H), 3.60-3.77(m, 4H), 7.32(d, 2H, J=8.3Hz), 7.85(br, 2H), 7.58(d, 2H, J=8.3Hz), 8.16(s, 1H), 9.32(br, 2H)	DMSO-d6, 300MHz
2-112		>250	1.31-1.58(m, 4H), 1.60(s, 6H), 1.82-1.91(m, 2H), 2.06-2.16(m, 2H), 2.53-2.65(m, 1H), 2.77-2.88(m, 1H), 3.30(s, 2H), 6.93(brs, 2H), 7.31(d, 2H, J=6.0Hz), 7.64(d, 2H, J=6.0Hz), 7.94(s, 1H), 12.40(brs, 1H)	DMSO-d6, 300
2-113		172 - 173	1.04-1.13(m, 2H), 1.34-1.46(m, 2H), 1.59(s, 6H), 1.78-1.84(m, 5H), 2.23(s, 3H), 2.36(d, 2H, J=6.0Hz), 2.51-2.58(m, 1H), 6.58(s, 1H), 6.92(brs, 2H), 7.28(d, 2H, J=8.0Hz), 7.62(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-114		250	1.04-1.22(m, 2H), 1.16(d, 6H, J=6.1Hz), 1.38-1.66(m, 4H), 1.60(s, 6H), 1.80-1.97(m, 5H), 2.46-2.62(m, 1H), 2.63-2.70(m, 1H), 6.93(br, 2H), 7.31(d, 2H, J=8.4Hz), 7.66(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-115		127 - 135	0.99-1.23(m, 6H), 1.17(t, 3H, J=7.1Hz), 1.38-1.52(m, 2H), 1.60(s, 6H), 1.72-1.94(m, 6H), 2.45-2.59(m, 1H), 2.78-2.94(m, 2H), 3.81-3.89(m, 2H), 4.02(q, 2H, J=7.1Hz), 6.93(br, 2H), 7.30(d, 2H, J=8.4Hz), 7.64(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz

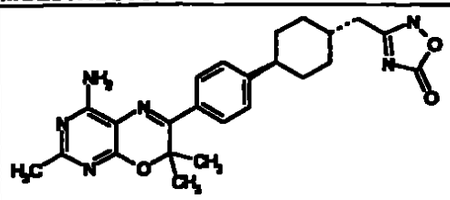
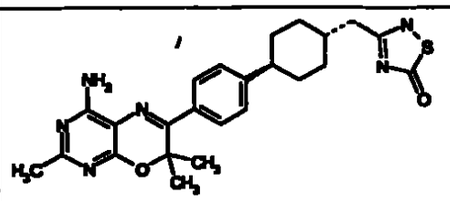
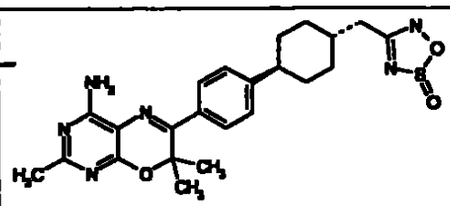
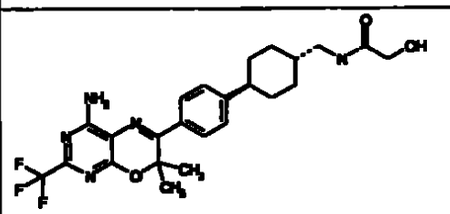
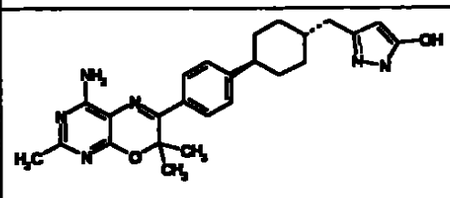
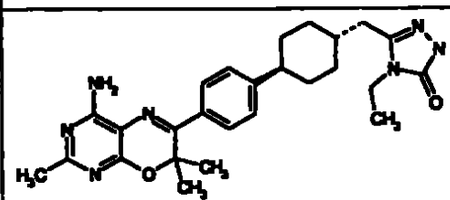
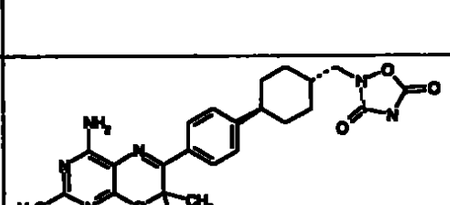
New Ex. No.	MOLSTRUCTURE	m.p	NMR(δ)	solvent
2-116		>250	0.93-1.22(m, 6H), 1.32-1.52(m, 4H), 1.60(s, 6H), 1.74-1.95(m, 7H), 2.20-2.34(m, 1H), 2.41(d, 2H, J=6.4Hz), 2.47-2.58(m, 1H), 3.27-3.39(m, 1H), 4.44(d, 1H, J=4.8Hz), 6.95(br, 2H), 7.28(d, 2H, J=8.3Hz), 7.63(d, 2H, J=8.3Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-117		>250	1.07-1.18(m, 2H), 1.43-1.53(m, 2H), 1.55(s, 6H), 1.70-1.85(m, 5H), 2.15(d, 2H, J=8.0Hz), 2.51-2.55(m, 1H), 6.21(brs, 2H), 6.31(d, 1H, J=8.0Hz), 7.29(d, 2H, J=8.0Hz), 7.49(d, 1H, J=8.0Hz), 7.60(d, 2H, J=8.0Hz), 11.94(brs, 1H)	DMSO-d6, 400MHz
2-118		215 - 218	1.08-1.23(m, 2H), 1.38-1.50(m, 2H), 1.59(s, 6H), 1.68-1.83(m, 5H), 2.52-2.55(m, 1H), 2.68(d, 2H, J=4.0Hz), 2.82(s, 3H), 6.95(brs, 2H), 7.06(s, 1H), 7.28(d, 2H, J=8.0Hz), 7.62(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-119		>250	1.08-1.18(m, 2H), 1.28(s, 9H), 1.35-1.49(m, 2H), 1.60(s, 6H), 1.75-1.85(m, 5H), 2.38(d, 2H, J=4.0Hz), 2.52-2.58(m, 1H), 6.55(brs, 1H), 6.94(brs, 2H), 7.29(d, 2H, J=12.0Hz), 7.62(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-120		226 - 227	0.68-1.19(m, 7H), 1.36-1.54(m, 2H), 1.59(s, 6H), 1.74-1.88(m, 5H), 2.33(d, 2H, J=4.0Hz), 2.53-2.69(m, 1H), 6.50(s, 1H), 6.94(brs, 2H), 7.28(d, 2H, J=8.0Hz), 7.62(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-121			1.14-1.34(m, 2H), 1.37-1.58(m, 3H), 1.60(s, 6H), 1.80-1.95(m, 5H), 2.51(m, 1H), 2.71(d, 2H, J=6.3 Hz), 3.77(s, 3H), 6.74(dd, 1H, J=2.2, 8.4 Hz), 6.91(brs, 2H), 6.99(d, 1H, J=2.2 Hz), 7.30(d, 2H, J=8.3 Hz), 7.35(d, 1H, J=8.4 Hz), 7.64(d, 2H, J=8.3 Hz), 7.95(s, 1H), 12.05(brs, 1H).	DMSO-d6, 300MHz
2-122		>230	1.15-1.33(m, 2H), 1.37-1.58(m, 3H), 1.60(s, 6H), 1.80-1.95(m, 5H), 2.51(m, 1H), 2.75(d, 2H, J=6.3 Hz), 6.92(brs, 2H), 7.14(d, 1H, J=8.4 Hz), 7.30(d, 2H, J=8.3 Hz), 7.39-7.55(m, 2H), 7.63(d, 2H, J=8.3 Hz), 7.95(s, 1H), 12.37(brs, 1H).	DMSO-d6, 300MHz

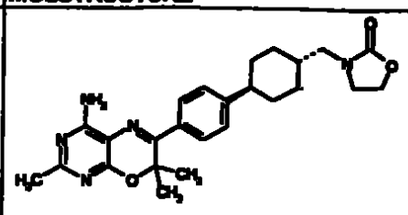
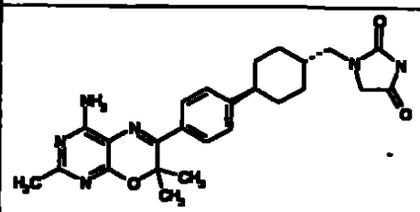
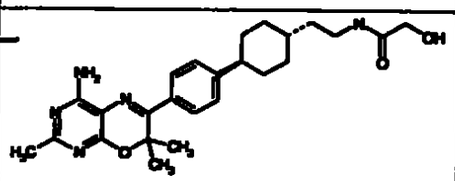
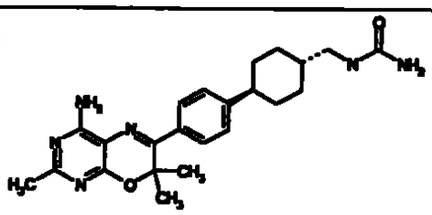
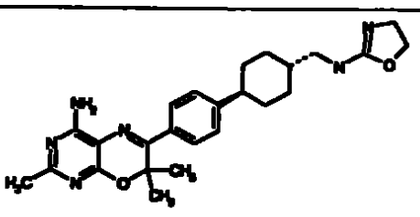
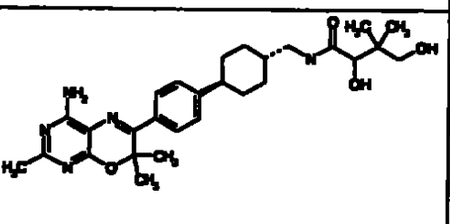
New Ex. No.	MOLSTRUCTURE	m.p	NMR(δ)	solvent
2-123		230 - 231	1.09-1.19(m, 2H), 1.41-1.52(m, 2H), 1.59(s, 6H), 1.76-1.86(m, 5H), 2.53-2.58(m, 1H), 3.18(d, 2H, J=12.0Hz), 6.71(brs, 1H), 6.93(brs, 2H), 7.27-7.42(m, 5H), 7.62(d, 2H, J=6.0Hz), 7.88(d, 2H, J=6.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-124		>230	1.14-1.33(m, 2H), 1.37-1.58(m, 3H), 1.60(s, 6H), 1.70-2.03(m, 5H), 2.51(m, 1H), 2.73(d, 2H, J=7.0 Hz), 6.72-7.13(m, 3H), 7.17-7.35(m, 3H), 7.44(brs, 1H), 7.62(d, 2H, J=8.3 Hz), 7.93(s, 1H), 12.30(brs, 1H).	DMSO-d6, 400MHz
2-125			0.97-1.11(m, 2H), 1.34-1.54(m, 12H), 1.60(s, 6H), 1.78-1.95(m, 4H), 2.53-2.58(m, 1H), 2.76-2.83(m, 2H), 6.94(brs, 2H), 7.30(d, 2H, J=9.0Hz), 7.57(brs, 1H), 7.65(d, 2H, J=9.0Hz), 7.95(s, 1H), 10.76(brs, 1H)	DMSO-d6, 300
2-126		234 - 235	0.93-1.50(m, 4H), 1.60(s, 6H), 1.72-1.91(m, 5H), 2.16(d, 2H, J=6.0Hz), 2.57-2.58(m, 1H), 6.95(brs, 2H), 7.29(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.95(s, 1H), 11.94(brs, 1H)	DMSO-d6, 300
2-127		228 - 230	1.03-1.17(m, 2H), 1.39-1.51(m, 2H), 1.58-1.67(m, 7H), 1.82-1.95(m, 4H), 2.09(s, 3H), 2.51-2.59(m, 1H), 3.06-3.10(m, 2H), 6.11(brs, 1H), 6.94(brs, 2H), 7.31(d, 2H, J=9.0Hz), 7.45-7.49(m, 1H), 7.65(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-128		253 - 254	0.98-1.13(m, 2H), 1.38-1.51(m, 3H), 1.60(s, 6H), 1.77-1.99(m, 7H), 2.52-2.58(m, 1H), 2.91-2.95(m, 2H), 6.93(brs, 2H), 7.30(d, 2H, J=8.0Hz), 7.63(d, 2H, J=8.0Hz), 7.82(t, 1H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-129		206 - 207	0.93-1.08(m, 2H), 1.32-1.47(m, 3H), 1.60(s, 6H), 1.76-1.85(m, 4H), 2.38(s, 3H), 2.51-2.54(m, 1H), 2.57-2.62(m, 2H), 6.93(brs, 2H), 7.29(d, 2H, J=9.0Hz), 7.41(d, 2H, J=9.0Hz), 7.54(t, 1H, J=8.0Hz), 7.64(d, 2H, J=9.0Hz), 7.69(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300

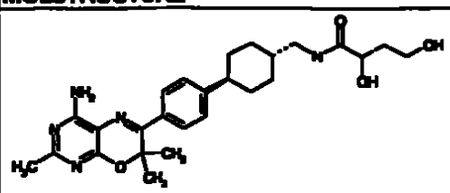
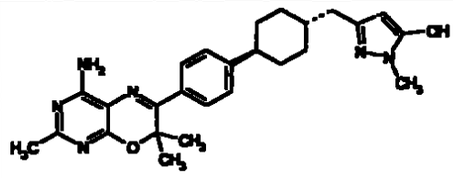
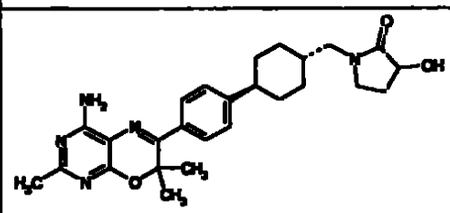
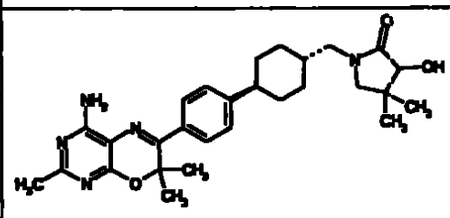
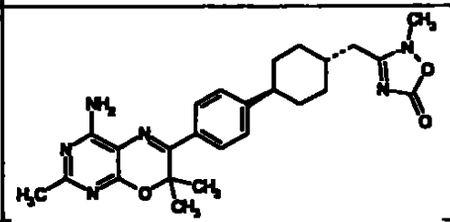
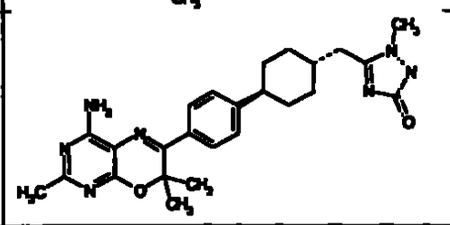
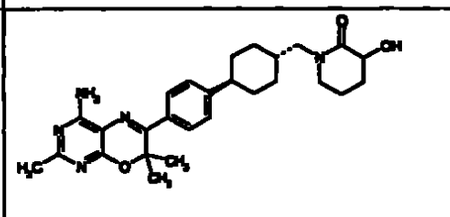
New Ex. No.	MOLSTRUCTURE	m.p	NMR(δ)	solvent
2-130		226 - 227	0.96-1.11(m, 2H), 1.37-1.55(m, 3H), 1.60(s, 6H), 1.79-1.96(m, 4H), 2.53-2.57(m, 1H), 2.74-2.79(m, 2H), 6.43(s, 2H), 6.50(t, 1H, J=6.0Hz), 6.93(brs, 2H), 7.31(d, 2H, J=9.0Hz), 7.85(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-131		230 - 231	0.99-1.13(m, 2H), 1.35-2.01(m, 18H), 2.51-2.58(m, 1H), 2.77-2.86(m, 2H), 2.96-3.01(m, 2H), 3.49-3.53(m, 1H), 6.93(brs, 2H), 7.30(d, 2H, J=9.0Hz), 7.84(d, 2H, J=9.0Hz), 7.91-7.97(m, 2H)	DMSO-d6, 300
2-132		217 - 218	0.98-1.14(m, 2H), 1.37-1.68(m, 16H), 2.53-2.58(m, 1H), 2.72-2.85(m, 2H), 2.96-3.00(m, 2H), 3.71(t, 1H, J=7.5Hz), 4.16(brs, 1H), 4.85(brs, 1H), 6.93(brs, 2H), 7.30(d, 2H, J=9.0Hz), 7.84(d, 2H, J=9.0Hz), 7.94-7.98(m, 2H)	DMSO-d6, 300
2-133		>230	1.61(s, 6H), 1.60-1.75(m, 6H), 2.16(m, 1H), 2.37(d, 2H, J=7.2 Hz), 2.80(m, 1H), 6.94(brs, 2H), 7.34(d, 2H, J=8.3 Hz), 7.84(d, 2H, J=8.3 Hz), 7.95(s, 1H).	DMSO-d6, 300MHz
2-134		225 - 228	1.07-1.18(m, 2H), 1.42-1.53(m, 2H), 1.58(s, 6H), 1.77-1.85(m, 5H), 1.91(s, 3H), 2.20(d, 2H, J=4.0Hz), 2.24(s, 3H), 2.54-2.57(m, 1H), 3.22(s, 3H), 6.81(brs, 2H), 7.28(d, 2H, J=8.0Hz), 7.81(d, 2H, J=12.0Hz), 11.86 and 11.93(brs, 1H)	DMSO-d6, 400MHz
2-135		229 - 230	1.01-1.13(m, 2H), 1.17(s, 6H), 1.41-1.51(m, 2H), 1.58(s, 6H), 1.68-1.84(m, 5H), 1.98(d, 2H, J=6.0Hz), 2.24(s, 3H), 2.52-2.56(m, 1H), 3.38(d, 2H, J=4.0Hz), 4.90(t, 1H, J=4.0Hz), 6.80(brs, 2H), 7.26(brs, 1H), 7.28(d, 2H, J=8.0Hz), 7.80(d, 2H, J=8.0Hz)	DMSO-d6, 400MHz
2-136		210 - 211	1.07-1.19(m, 2H), 1.42-1.52(m, 2H), 1.58(s, 6H), 1.76-1.86(m, 5H), 2.12(d, 2H, J=8.0Hz), 2.24(s, 3H), 2.51-2.55(m, 1H), 3.15-3.26(m, 2H), 3.35-3.39(m, 1H), 3.54-3.58(m, 1H), 3.95-4.08(m, 2H), 4.57(d, 1H, J=4.0Hz), 4.95(d, 1H, J=4.0Hz), 6.80(brs, 2H), 7.28(d, 2H, J=8.0Hz), 7.80(d, 2H, J=8.0Hz)	DMSO-d6, 400MHz

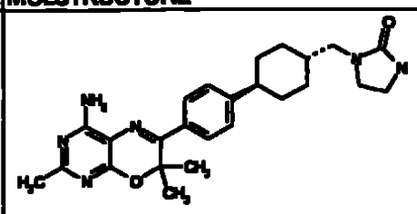
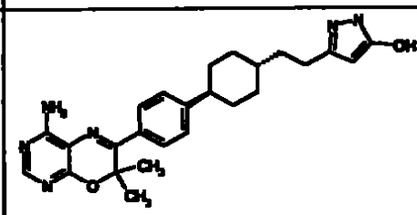
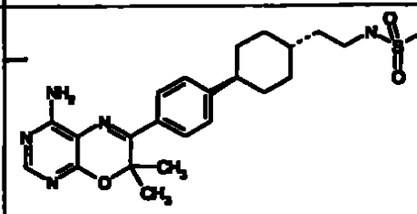
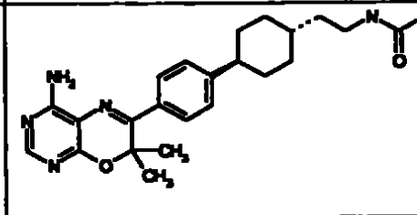
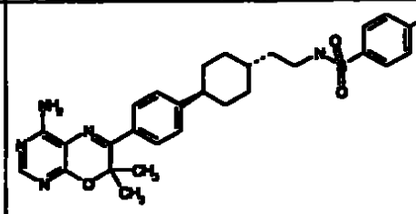
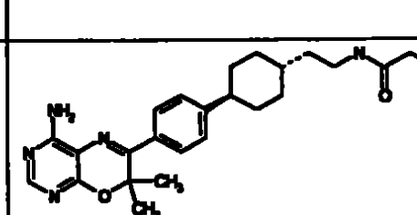
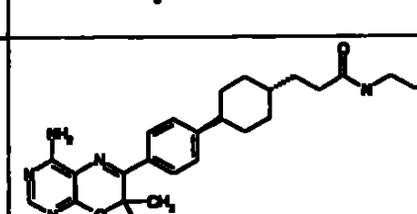
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-137		>250	1.13-1.24(m, 2H), 1.38-1.50(m, 2H), 1.57(s, 6H), 1.73-1.83(m, 5H), 2.24(s, 3H), 2.82(d, 2H, J=6.0Hz), 3.35-3.39(m, 1H), 6.81(brs, 2H), 7.27(d, 2H, J=8.0Hz), 7.80(d, 2H, J=8.0Hz)	DMSO-d6, 400MHz
2-138		235 - 238	0.96-1.13(m, 2H), 1.35-1.55(m, 3H), 1.58(s, 6H), 1.75-1.89(m, 4H), 2.24(s, 3H), 2.47-2.61(m, 1H), 3.01(t, 2H, J=6.0Hz), 3.80(d, 2H, J=6.0Hz), 5.42(t, 1H, J=6.0Hz), 6.82(br, 2H), 7.29(d, 2H, J=8.3Hz), 7.81(d, 2H, J=8.3Hz), 7.89(t, 1H, J=6.0Hz)	DMSO-d6, 300MHz
2-139		249 - 250	1.03(s, 6H), 1.06-1.08(m, 2H), 1.36-1.48(m, 3H), 1.58(s, 6H), 1.81(m, 4H), 2.25(s, 3H),2.86(m, 2H), 3.37(d, 2H, J=5.3Hz), 4.86(t, 1H, J=5.3Hz),6.80(brs, 2H), 7.29(d, 2H, J=8.3Hz), 7.44(t, 1H, J=5.8Hz), 7.82(d, 2H, J=8.3Hz).	DMSO-d6, 300MHz
2-140		223 - 224	0.96-1.10(m, 2H), 1.37-1.48(m, 3H), 1.58(s, 6H), 1.82(m, 4H), 2.25(s, 3H), 2.25(t, 2H, J=6.5Hz), 2.95(m, 2H), 3.61(dt, 1H, J=6.5Hz, 5.3Hz), 4.53(t, 1H, J=5.3Hz), 6.80(brs, 2H), 7.29(d, 2H, J=8.3Hz), 7.81(d, 2H, J=8.3Hz). 7.78(t, 1H, J=5.3Hz),	DMSO-d6, 300MHz
2-141		221 - 223	0.97- 1.15 (m, 2 H), 1.24 (s, 6 H), 1.25- 1.53 (m, 5 H), 1.58 (s, 6 H), 1.76- 1.93 (m, 4 H), 2.25 (s, 3 H), 2.45- 2.62 (m, 1 H), 3.12 (q, J = 6.4 Hz, 2 H), 5.28 (s, 1 H), 6.83 (br s, 2 H), 7.28 (d, J = 8.3 Hz, 2 H), 7.53- 7.81 (m, 1 H), 7.81 (d, J = 8.3 Hz, 2 H).	DMSO-d6, 300 MHz
2-142		142 - 144	0.99-1.19(m, 2H), 1.34-1.58(m, 3H), 1.60(s, 6H), 1.67-1.89(m, 5H), 2.09(d, 2H, d=6.9 Hz), 2.24(s, 3H), 2.51(m, 1H), 3.83(d, 2H, J=5.5 Hz), 6.81(brs, 2H), 6.96(brs, 1H), 7.24(brs, 1H), 7.30(d, 2H, J=8.3 Hz), 7.82(d, 2H, J=8.3 Hz), 7.95(t, 1H, J=5.5 Hz).	DMSO-d6, 300MHz
2-143		196 - 198	a mixture of 2 conformers; 1.02-1.22(m, 2H), 1.34-1.58(m, 3H), 1.58(s, 6H), 1.72-1.92(m, 5H), 2.13 and 2.27(d, 2H, d=6.9 Hz), 2.24(s, 3H), 2.51(m, 1H), 2.81 and 3.03(s, 3H), 3.98 and 4.09(s, 2H), 6.82(brs, 2H), 7.28(d, 2H, J=8.3 Hz), 7.82(d, 2H, J=8.3 Hz) 11.70(brs, 1H).	DMSO-d6, 300MHz

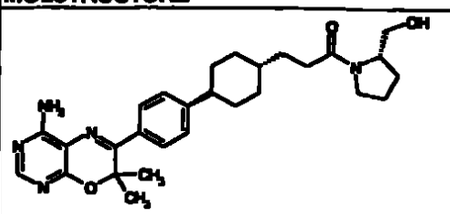
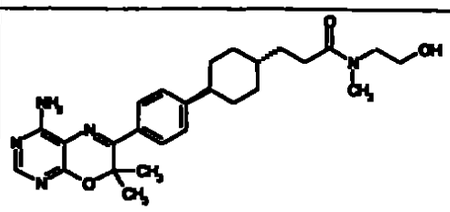
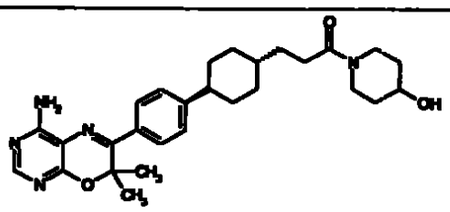
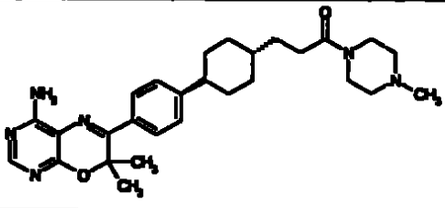
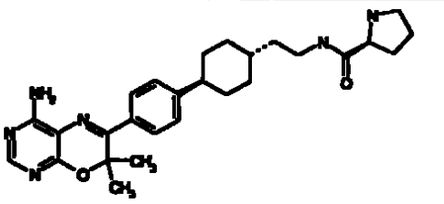
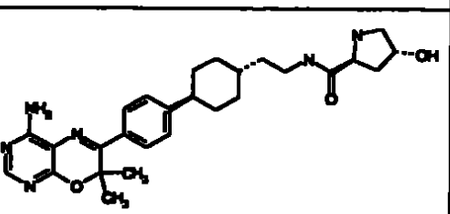
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-144		>230	a mixture of 2 conformers; 0.99-1.20(m, 2H), 1.34-1.58(m, 3H), 1.58(s, 6H), 1.73-1.92(m, 5H), 2.12 and 2.26(d, 2H, d=6.9 Hz), 2.24(s, 3H), 2.51(m, 1H), 2.79 and 3.98(s, 3H), 3.85 and 3.92(s, 2H), 6.82(brs, 2H), 6.96 and 7.14(brs, 1H), 7.29(d, 2H, J=8.3 Hz), 7.27 and 7.43(brs, 1H), 7.81(d, 2H, J=8.3 Hz).	DMSO-d6, 400MHz
2-145		>250	0.55(s, 3H), 1.21(s, 3H), 1.55(s, 6H), 1.95-2.02(m, 1H), 2.14-2.36(m, 4H), 2.24(s, 3H), 3.14-3.20(m, 1H), 6.83(brs, 2H), 7.16(d, 2H, J=8.0Hz), 7.82(d, 2H, J=8.0Hz)	DMSO-d6, 400MHz
2-148		>250	1.58(s, 6H), 1.74-1.92(m, 2H), 2.24(s, 3H), 2.37(d, 2H, J=8.0Hz), 2.44-2.60(m, 4H), 3.36-3.43(m, 1H), 6.80(brs, 2H), 7.27(d, 2H, J=8.0Hz), 7.81(d, 2H, J=8.0Hz), 11.98(brs, 1H)	DMSO-d6, 400MHz
2-147		>230	1.05-1.20(m, 2H), 1.38-1.52(m, 2H), 1.58(s, 6H), 1.73-1.87(m, 5H), 2.24(s, 3H), 2.29(d, 2H, d=6.9 Hz), 2.51(m, 1H), 6.81(brs, 2H), 7.28(d, 2H, J=8.3 Hz), 7.81(d, 2H, J=8.3 Hz), 11.07(s, 1H), 11.10(brs, 1H).	DMSO-d6, 400MHz
2-148		>250	1.13-1.24(m, 2H), 1.43-1.55(m, 2H), 1.58(s, 6H), 1.82-1.85(m, 4H), 2.24(s, 3H), 2.38-2.41(m, 2H), 2.50-2.58(m, 1H), 6.82(br, 1H), 7.30(d, 2H, J=8.0Hz), 7.82(d, 2H, J=8.0Hz), 11.96(brs, 1H), 15.85(br, 1H)	DMSO-d6, 300MHz
2-149		237 - 238	1.58(s, 6H), 1.60-1.71(m, 4H), 2.04-2.23(m, 3H), 2.23(s, 3H), 2.24(s, 3H), 2.40-2.46(m, 2H), 3.35-3.41(m, 1H), 6.81(brs, 2H), 7.25(d, 2H, J=8.0Hz), 7.81(d, 2H, J=8.0Hz), 11.99(brs, 1H)	DMSO-d6, 400MHz
2-150		228 - 229	0.99-1.10(m, 2H), 1.25(s, 6H), 1.37-1.48(m, 2H), 1.58(s, 6H), 1.76-1.85(m, 5H), 2.24(s, 3H), 2.53-2.57(m, 1H), 2.96-2.99(m, 2H), 5.32(s, 1H), 6.81(brs, 2H), 7.28(d, 2H, J=8.0Hz), 7.88(brs, 1H), 7.90(d, 2H, J=8.0Hz)	DMSO-d6, 400MHz

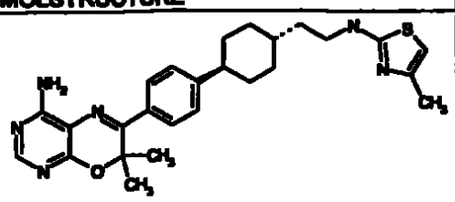
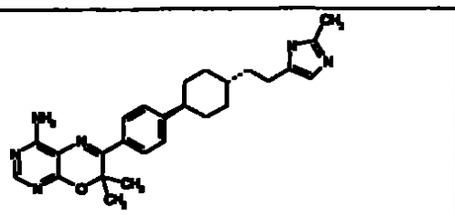
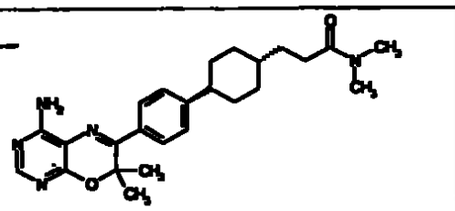
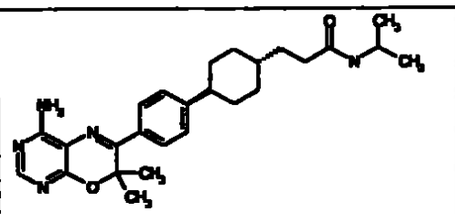
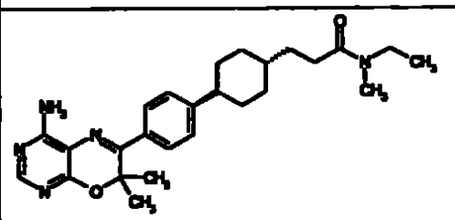
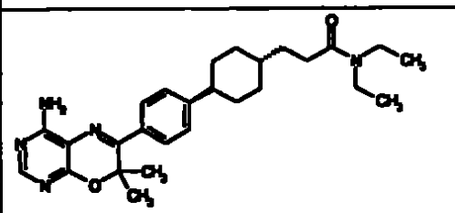
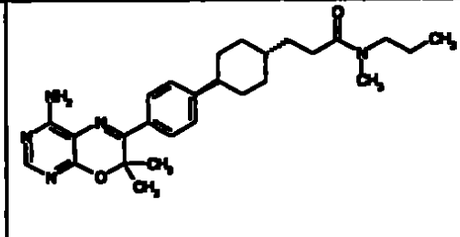
New Ex. No.	MOLSTRUCTURE	m p	NMR(δ)	solvent
2-151		>250	1.11-1.23(m, 2H), 1.42-1.52(m, 2H), 1.57(s, 6H), 1.77-1.86(m, 5H), 2.25(s, 3H), 2.44(d, 2H, J=6.0Hz), 2.53-2.62(m, 1H), 6.81(brs, 2H), 7.28(d, 2H, J=8.0Hz), 7.81(d, 2H, J=8.0Hz), 12.70(brs, 1H)	DMSO-d6, 400MHz
2-152		225 - 226	1.11-1.23(m, 2H), 1.41-1.49(m, 2H), 1.57(s, 6H), 1.76-1.84(m, 5H), 2.24(s, 3H), 2.44(d, 2H, J=6.0Hz), 2.53-2.61(m, 1H), 6.82(brs, 2H), 7.28(d, 2H, J=8.0Hz), 7.81(d, 2H, J=8.0Hz), 12.69(brs, 1H)	DMSO-d6, 400MHz
2-153			1.11-1.24(m, 2H), 1.40-1.51(m, 2H), 1.58(s, 6H), 1.77-1.87(m, 5H), 2.24(s, 3H), 2.46(d, 2H, J=8.0Hz), 2.52-2.58(m, 1H), 6.81(brs, 2H), 7.28(d, 2H, J=8.0Hz), 7.81(d, 2H, J=8.0Hz), 11.41(brs, 1H)	DMSO-d6, 400MHz
2-154		229 - 233	1.00-1.11(m, 2H), 1.37-1.58(m, 3H), 1.65(s, 6H), 1.76-1.87(m, 4H), 2.49-2.57(m, 1H), 2.99-3.04(m, 2H), 3.81(d, 2H, J=6.0Hz), 5.42(t, 1H, J=6.0Hz), 7.32(d, 2H, J=8.0Hz), 7.69(d, 2H, J=8.0Hz)	DMSO-d6, 300MHz
2-155			1.01-1.22(m, 2H), 1.34-1.52(m, 2H), 1.57(s, 6H), 1.68-1.89(m, 4H), 2.24(s, 3H), 2.37(d, 2H, d=6.9 Hz), 2.50(m, 1H), 5.23(s, 1H), 6.81(brs, 2H), 7.27(d, 2H, J=8.3 Hz), 7.80(d, 2H, J=8.3 Hz), 9.25(brs, 1H), 11.20(brs, 1H).	DMSO-d6, 400MHz
2-156		>250	1.09-1.23(m, 2H), 1.15(t, 3H, J=8.0Hz), 1.43-1.52(m, 2H), 1.57(s, 6H), 1.71-1.90(m, 5H), 2.24(s, 3H), 2.44(d, 2H, J=8.0Hz), 2.53-2.59(m, 1H), 3.58(q, 2H, J=8.0Hz), 6.80(brs, 2H), 7.28(d, 2H, J=8.0Hz), 7.80(d, 2H, J=8.0Hz). 11.34(s, 1H)	DMSO-d6, 400MHz
2-157			1.11-1.24(m, 2H), 1.44-1.54(m, 2H), 1.58(s, 6H), 1.88-1.87(m, 5H), 2.24(s, 3H), 2.53-2.57(m, 1H), 3.51(d, 2H, J=8.0Hz), 6.80(brs, 2H), 7.29(d, 2H, J=8.0Hz), 7.81(d, 2H, J=8.0Hz), 12.28(brs, 1H)	DMSO-d6, 400MHz

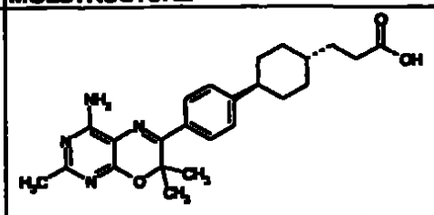
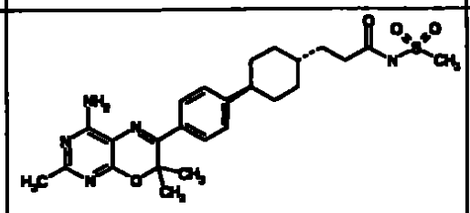
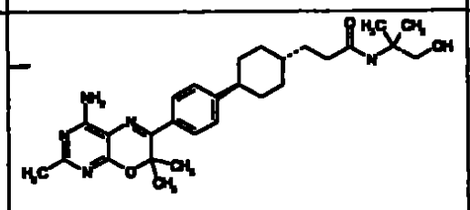
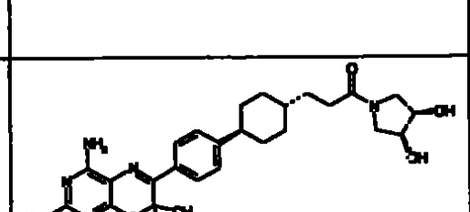
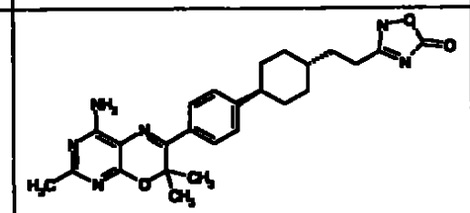
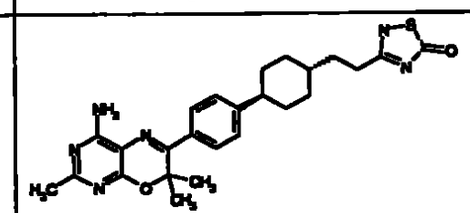
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-158		240-241	1.03-1.14(m, 2H), 1.41-1.53(m, 2H), 1.58-1.71(m, 1H), 1.58(s, 6H), 1.77-1.88(m, 4H), 2.25(s, 3H), 2.50-2.58(m, 1H), 3.04(d, 2H, J=9.0Hz), 3.88(t, 2H, J=7.5Hz), 4.27(t, 2H, J=7.5Hz), 6.80(br, 1H), 7.29(d, 2H, J=8.0Hz), 7.63(d, 2H, J=9.0Hz)	DMSO-d6, 300MHz
2-159		148(dec.)	1.01-1.13(m, 2H), 1.39-1.51(m, 2H), 1.58-1.88(m, 1H), 1.58(s, 6H), 1.76-1.88(m, 4H), 2.25(s, 3H), 2.50-2.57(m, 1H), 3.11(d, 2H, J=6.0Hz), 3.95(s, 2H), 6.81(br, 1H), 7.29(d, 2H, J=9.0Hz), 7.62(d, 2H, J=8.0Hz)	DMSO-d6, 300MHz
2-160		185-186	1.00-1.13(m, 2H), 1.30-1.51(m, 6H), 1.58(s, 6H), 1.79-1.87(m, 4H), 2.24(s, 3H), 2.50-2.58(m, 1H), 0.00-0.00(m, 2H), 3.17(q, 2H, J=7.0Hz), 3.78(d, 2H, J=6.0Hz),, 6.40(t, 1H, J=6.0Hz), 6.80(br, 2H), 7.29(d, 2H, J=9.0Hz), 7.62(d, 2H, J=9.0Hz), 7.88(t, 1H, J=6.0Hz)	DMSO-d6, 300MHz
2-161		219 - 221	0.95-1.12(m, 2H), 1.35-1.52(m, 3H), 1.58(s, 6H), 1.73-1.91(m, 4H), 2.24(s, 3H), 2.47-2.57(m, 1H), 2.86(t, 2H, J=6.2Hz), 5.33(br, 2H), 6.98(t, 1H, J=5.7Hz), 6.80(br, 2H), 7.29(d, 2H, J=8.3Hz), 7.61(d, 2H, J=8.3Hz)	DMSO-d6, 300MHz
2-162		216 - 250	0.95-1.11(m, 2H), 1.36-1.53(m, 3H), 1.58(s, 6H), 1.76-1.90(m, 4H), 2.24(s, 3H), 2.45-2.58(m, 1H), 2.91(d, 2H, J=6.8Hz), 3.58(t, 2H, J=8.5Hz), 4.13(t, 2H, J=8.5Hz), 6.78(br, 2H), 7.29(d, 2H, J=8.3Hz), 7.61(d, 2H, J=8.3Hz)	DMSO-d6, 300MHz
2-163		219 - 221	0.82(s, 3H), 0.83(s, 3H), 0.95-1.14(m, 2H), 1.35-1.54(m, 3H), 1.58(s, 6H), 1.76-1.88(m, 4H), 2.24(s, 3H), 2.44-2.58(m, 1H), 2.94-3.10(m, 2H), 3.16-3.34(m, 2H), 3.73(d, 1H, J=5.7Hz), 4.48(t, 1H, J=5.7Hz), 5.31(d, 1H, J=5.7Hz), 6.79(br, 2H), 7.29(d, 2H, J=8.3Hz), 7.61(d, 2H, J=8.3Hz), 7.88(t, 1H, J=5.8Hz)	DMSO-d6, 300MHz

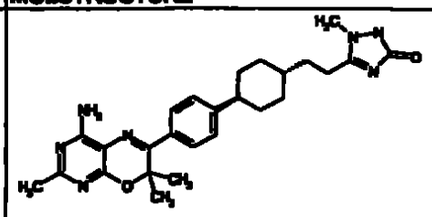
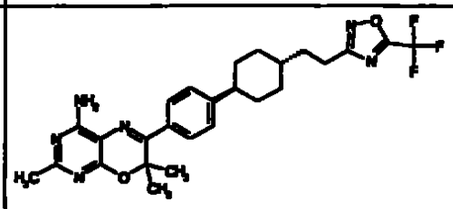
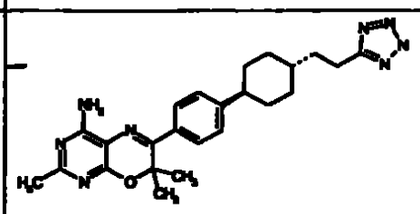
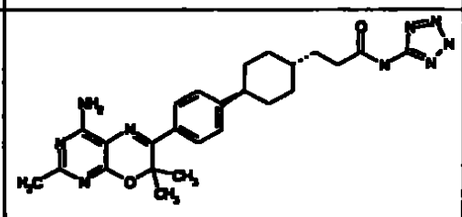
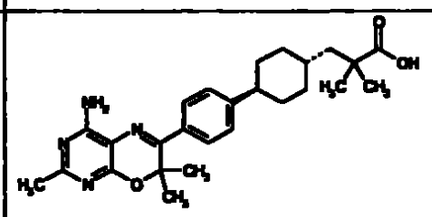
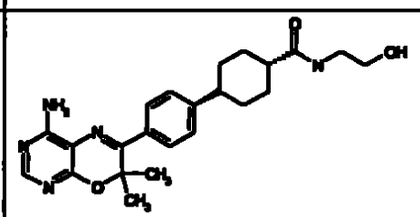
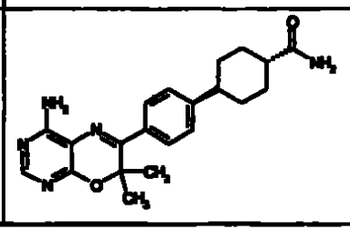
New Ex. No.	MOLSTRUCTURE	m p	NMR(δ)	solvent
2-164		222 - 225	0.98-1.14(m, 2H), 1.35-1.61(m, 4H), 1.58(s, 6H), 1.75-1.89(m, 5H), 2.24(s, 3H), 2.48-2.59(m, 1H), 2.99(t, 2H, J=6.5Hz), 3.45-3.54(m, 2H), 3.95(dt, 1H, J=5.7, 3.9Hz), 4.42(t, 1H, J=5.7Hz), 5.39(d, 1H, J=5.7Hz), 6.81(br, 2H), 7.29(d, 2H, J=8.3Hz), 7.61(d, 2H, J=8.3Hz), 7.66(t, 1H, J=8.2Hz)	DMSO-d6, 300MHz
2-165		>250	a mixture of 2 conformers;1.02-1.15(m, 2H), 1.37-1.48(m, 2H), 1.57(s, 6H), 1.76-1.85(m, 5H), 2.24(s, 3H), 2.27(d, 2H, J=4.0Hz), 2.52-2.55(m, 1H), 3.30 and 3.58(s, 3H), 5.12(bra, 1H), 6.81(bra, 2H), 7.27(d, 2H, J=8.0Hz), 7.60(d, 2H, J=8.0Hz), 10.84(bra, 1H)	DMSO-d6, 400MHz
2-166		225 - 233	0.98-1.13(m, 2H), 1.35-1.51(m, 2H), 1.58(s, 6H), 1.83-1.87(m, 6H), 2.21-2.32(m, 1H), 2.24(s, 3H), 2.45-2.60(m, 1H), 3.06(d, 2H, J=7.1Hz), 3.17-3.35(m, 2H), 4.04-4.16(m, 1H), 5.45(br, 1H), 6.82(br, 2H), 7.29(d, 2H, J=8.3Hz), 7.62(d, 2H, J=8.3Hz)	DMSO-d6, 300MHz
2-167			0.90(s, 3H), 0.99-1.14(m, 2H), 1.08(s, 3H), 1.30-1.51(m, 2H), 1.58(s, 6H), 1.82-1.90(m, 5H), 2.24(s, 3H), 2.45-2.59(m, 1H), 2.95-3.12(m, 4H), 3.74(d, 1H, J=5.7Hz), 5.41(d, 1H, J=5.7Hz), 6.79(br, 2H), 7.28(d, 2H, J=8.3Hz), 7.61(d, 2H, J=8.3Hz)	DMSO-d6, 300MHz
2-168			1.13-1.31(m, 2H), 1.38-1.58(m, 2H), 1.58(s, 6H), 1.74-1.92(m, 5H), 2.25(s, 3H), 2.50(m, 1H), 2.56(d, 2H, d=6.9 Hz), 3.72(s, 3H), 6.80(bra, 2H), 7.29(d, 2H, J=8.3 Hz), 7.62(d, 2H, J=8.3 Hz).	DMSO-d6, 300MHz
2-169		>230	1.10-1.25(m, 2H), 1.38-1.53(m, 2H), 1.57(s, 6H), 1.89-1.97(m, 5H), 2.24(s, 3H), 2.50(m, 1H), 2.54(d, 2H, d=6.9 Hz), 3.58(s, 3H), 6.80(bra, 2H), 7.27(d, 2H, J=8.3 Hz), 7.60(d, 2H, J=8.3 Hz), 10.86(bra, 1H).	DMSO-d6, 400MHz
2-170		228 - 229	1.05-1.15(m, 2H), 1.38-1.48(m, 2H), 1.58(s, 6H), 1.86-2.01(m, 7H), 2.24(s, 3H), 2.51-2.55(m, 1H), 3.08-3.30(m, 6H), 3.85-3.90(m, 2H), 4.97(d, 1H, J=4.0Hz), 6.80(bra, 2H), 7.27(d, 2H, J=8.0Hz), 7.61(d, 2H, J=12.0Hz)	DMSO-d6, 400MHz

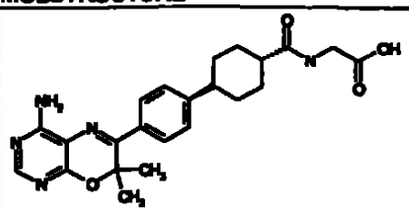
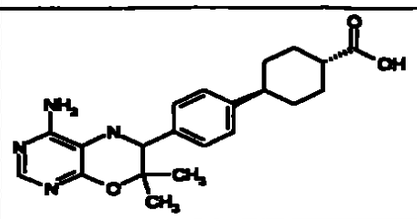
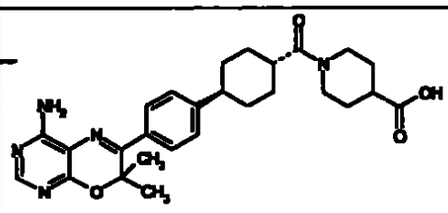
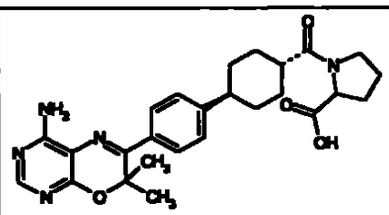
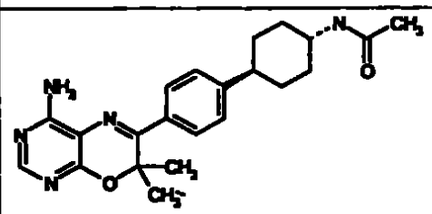
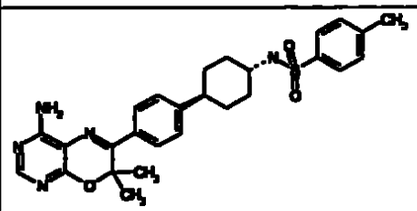
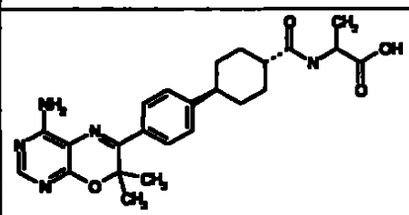
New Ex. No.	MOLSTRUCTURE	m p	NMR(δ)	solvent
2-171			1.08-1.28(m, 2H), 1.38-1.80(m, 3H), 1.69(s, 6H), 1.84-2.04(m, 4H), 2.44(s, 3H), 2.48-2.80(m, 1H), 3.09(d, 2H, J=8.0Hz), 3.38-3.53(m, 4H), 4.59(s, 1H), 5.50(br, 2H), 7.24(d, 2H, J=8.3Hz), 7.54(d, 2H, J=8.3Hz)	CDCl3, 300MHz
2-172		>250	1.04-1.09(m, 2H), 1.43(m, 1H), 1.43-1.50(m, 4H), 1.60(s, 6H), 1.80-1.90(m, 4H), 5.24(s, 1H), 6.68(brs, 2H), 7.29(d, 2H, J=8.3 Hz), 7.82(d, 2H, J=8.3 Hz), 7.94(s, 1H), 9.20(brs, 1H), 11.20(brs, 1H).	DMSO-d6, 400MHz
2-173		218 - 219	1.02-1.13(m, 2H), 1.40-1.49(m, 5H), 1.60(s, 6H), 1.81-1.88(m, 4H), 2.53-2.57(m, 1H), 2.89(s, 3H), 2.96-3.02(m, 2H), 6.86-6.97(m, 3H), 7.31(d, 2H, J=9.0Hz), 7.65(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-174		238 - 239	0.99-1.14(m, 2H), 1.31-1.52(m, 5H), 1.60(s, 6H), 1.79(s, 3H), 1.80-1.86(m, 4H), 2.53-2.59(m, 1H), 3.05-3.12(m, 2H), 6.93(brs, 2H), 7.30(d, 2H, J=9.0Hz), 7.95(d, 2H, J=8.0Hz), 7.77(t, 1H, J=4.5Hz), 7.95(s, 1H)	DMSO-d6, 300
2-175		230 - 231	0.91-1.08(m, 2H), 1.27-1.45(m, 5H), 1.60(s, 6H), 1.67-1.82(m, 4H), 2.39(s, 3H), 2.44-2.49(m, 1H), 2.74-2.80(m, 2H), 6.93(brs, 2H), 7.28(d, 2H, J=9.0Hz), 7.41(d, 2H, J=9.0Hz), 7.45(t, 1H, J=7.5Hz), 7.84(d, 2H, J=9.0Hz), 7.89(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-176		196 - 198	0.98-1.14(m, 2H), 1.29-1.85(m, 11H), 1.76-1.93(m, 4H), 2.51-2.69(m, 1H), 3.14-3.21(m, 2H), 3.79(d, 2H, J=6.0Hz), 5.39(t, 1H, J=6.0Hz), 6.92(brs, 2H), 7.30(d, 2H, J=9.0Hz), 7.82-7.87(m, 3H), 7.95(s, 1H)	DMSO-d6, 300
2-177		198 - 200	0.84(t, 3H, J=7.4Hz), 0.97-1.12(m, 2H), 1.18-1.53(m, 7H), 1.60(s, 6H), 1.76-1.88(m, 4H), 2.10(t, 2H, J=7.7Hz), 2.46-2.57(m, 1H), 2.99(q, 2H, J=6.5Hz), 6.94(br, 2H), 7.29(d, 2H, J=8.3Hz), 7.84(d, 2H, J=8.3Hz), 7.75(t, 1H, J=6.5Hz), 7.95(s, 1H)	DMSO-d6, 300MHz

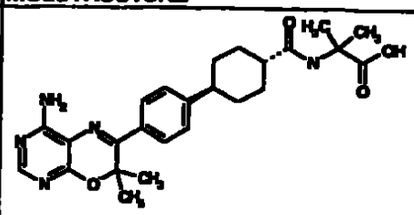
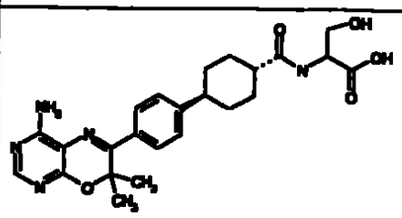
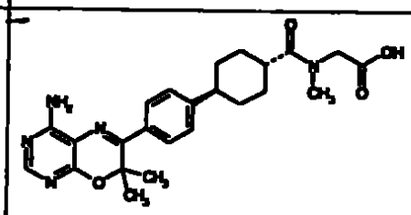
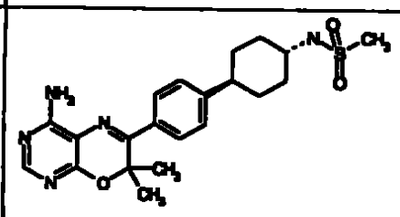
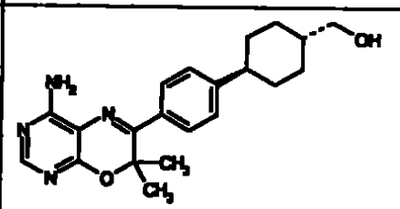
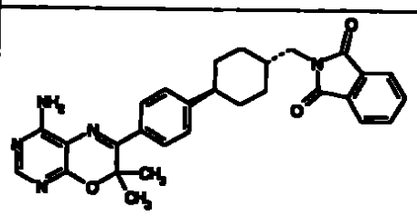
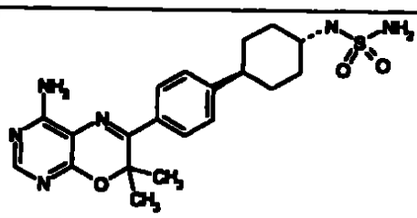
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-178		143 - 160	1.03-1.17(m, 2H), 1.25-1.56(m, 5H), 1.64(s, 6H), 2.30(t, 1.2H, J=7.7Hz), 2.39(t, 0.8H, J=7.7Hz), 2.51-2.62(m, 1H), 3.17-3.54(m, 5H), 3.89-4.00(m, 1H), 4.77(br, 0.6H), 4.95(br, 0.4H), 6.99(br, 2H), 7.33(d, 2H, J=8.3Hz), 7.87(d, 2H, J=8.3Hz), 7.98(s, 1H)	DMSO-d6, 300MHz
2-179		168 - 170	0.98-1.16(m, 2H), 1.25-1.55(m, 5H), 1.60(s, 6H), 1.75-1.94(m, 4H), 2.24-2.44(m, 2H), 2.48-2.60(m, 1H), 2.81(s, 1.5H), 3.00(s, 1.5H), 3.25-3.41(m, 2H), 3.43-3.55(m, 2H), 4.60(br, 0.5H), 4.78(br, 0.5H), 6.92(br, 2H), 7.30(d, 2H, J=8.4Hz), 7.84(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-180		200 - 202	0.98-1.55(m, 9H), 1.60(s, 6H), 1.81-1.94(m, 6H), 2.33(t, 2H, J=7.8Hz), 2.48-2.59(m, 1H), 2.90-3.04(m, 1H), 3.07-3.20(m, 1H), 3.60-3.75(m, 2H), 3.85-4.03(m, 1H), 4.71(br, 1H), 6.92(br, 2H), 7.30(d, 2H, J=8.4Hz), 7.84(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-181		83 - 207	1.02-1.14(m, 2H), 1.24-1.51(m, 5H), 1.60(s, 6H), 1.77-1.91(m, 4H), 2.16-2.37(m, 8H), 2.46-2.54(m, 1H), 3.38-3.50(m, 4H), 6.93(br, 2H), 7.29(d, 2H, J=8.3Hz), 7.84(d, 2H, J=8.3Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-182		167 - 169	0.98-1.13(m, 2H), 1.27-1.50(m, 6H), 1.55-1.69(m, 9H), 1.76-2.00(m, 5H), 2.51-2.57(m, 1H), 2.80-2.87(m, 2H), 3.09-3.16(m, 2H), 3.49-3.53(m, 1H), 6.94(brs, 2H), 7.29(d, 2H, J=8.0Hz), 7.83(d, 2H, J=8.0Hz), 7.88-7.92(m, 1H), 7.95(s, 1H)	DMSO-d6, 300
2-183		201 - 203	0.98-1.13(m, 2H), 1.24-1.70(m, 13H), 1.77-1.98(m, 5H), 2.51-2.58(m, 1H), 2.71-2.87(m, 2H), 3.07-3.16(m, 2H), 3.70(t, 1H, J=7.5Hz), 4.17(brs, 1H), 4.87(d, 1H, J=3.0Hz), 6.92(brs, 2H), 7.30(d, 2H, J=8.0Hz), 7.84(d, 2H, J=8.0Hz), 7.92(t, 1H, J=4.5Hz), 7.95(s, 1H)	DMSO-d6, 300

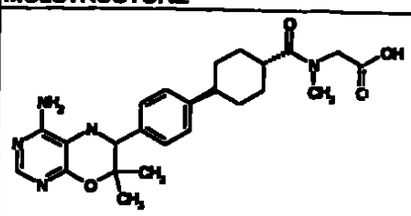
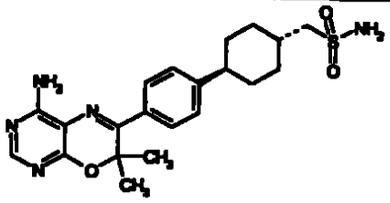
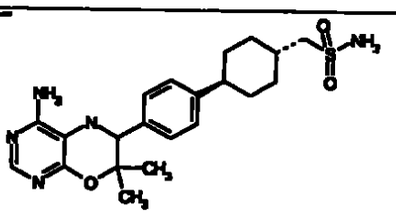
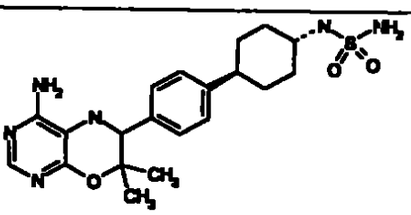
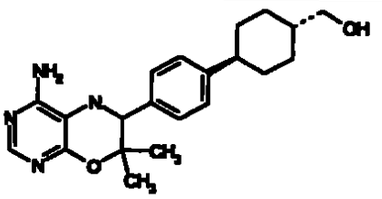
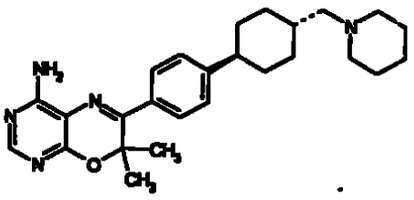
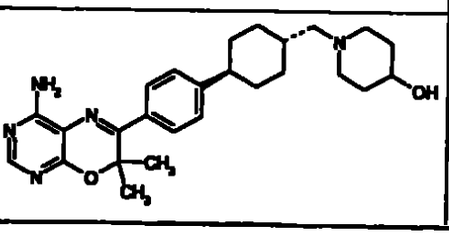
New Ex. No.	MOLSTRUCTURE	m p	NMR(δ)	solvent
2-184		>250	1.03-1.17(m, 2H), 1.37-1.54(m, 5H), 1.60(s, 6H), 1.78-1.90(m, 4H), 2.08(s, 3H), 2.53-2.59(m, 1H), 3.19-3.25(m, 2H), 6.12(brs, 1H), 6.94(brs, 2H), 7.30(d, 2H, J=8.0Hz), 7.34-7.39(m, 1H), 7.64(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-185		193 - 194	1.02-1.14(m, 2H), 1.27-1.51(m, 5H), 1.60(s, 6H), 1.80-1.89(m, 4H), 2.20(s, 3H), 2.44-2.48(m, 2H), 2.52-2.58(m, 1H), 6.53(s, 1H), 6.96(brs, 2H), 7.29(d, 2H, J=12.0Hz), 7.62(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-186		200 - 201	0.98-1.13(m, 2H), 1.25-1.51(m, 5H), 1.60(s, 6H), 1.77-1.90(m, 4H), 2.31(t, 2H, J=7.7Hz), 2.50-2.57(m, 1H), 2.81(s, 3H), 2.97(s, 3H), 6.93(br, 2H), 7.30(d, 2H, J=8.1Hz), 7.64(d, 2H, J=8.1Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-187		206 - 208	0.98-1.11(m, 2H), 1.04(d, 6H, J=6.6Hz), 1.20-1.51(m, 5H), 1.60(s, 6H), 1.76-1.92(m, 4H), 2.07(t, 2H, J=7.3Hz), 2.45-2.58(m, 1H), 3.83(dt, 1H, J=20.9, 6.6Hz), 6.93(br, 2H), 7.30(d, 2H, J=8.0Hz), 7.63(t, 1H, J=7.3Hz), 7.64(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-188		173 - 175	0.99(t, 1.5H, J=7.1Hz), 1.01-1.15(m, 2H), 1.10(t, 1.5H, J=7.1Hz), 1.22-1.54(m, 5H), 1.60(s, 6H), 1.76-1.87(m, 4H), 2.29(t, 1H, J=7.7Hz), 2.32(t, 1H, J=7.7Hz), 2.46-2.58(m, 1H), 2.78(s, 1.5H), 2.94(s, 1.5H), 3.28-3.37(m, 2H), 6.92(br, 2H), 7.30(d, 2H, J=8.4Hz), 7.64(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-189		192 - 194	0.98-1.13(m, 2H), 1.00(t, 3H, J=7.0Hz), 1.11(t, 3H, J=7.0Hz), 1.26-1.52(m, 5H), 1.60(s, 6H), 1.75-1.92(m, 4H), 2.30(t, 2H, J=7.7Hz), 2.49-2.59(m, 1H), 3.22-3.34(m, 4H), 6.94(br, 2H), 7.30(d, 2H, J=8.4Hz), 7.64(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-190		210-212	0.80(t, 1.5H, J=7.3Hz), 0.84(t, 1.5H, J=7.3Hz), 0.98-1.15(m, 2H), 1.22-1.57(m, 8H), 1.60(s, 6H), 1.74-1.91(m, 4H), 2.28-2.37(m, 2H), 2.47-2.59(m, 1H), 2.79(s, 1.5H), 2.95(s, 1.5H), 3.24(q, 2H, J=7.3Hz), 6.93(br, 2H), 7.30(d, 2H, J=8.4Hz), 7.64(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz

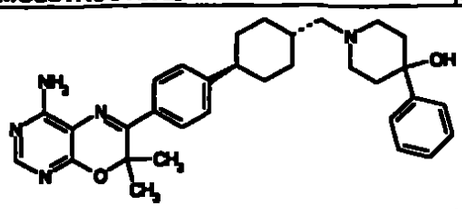
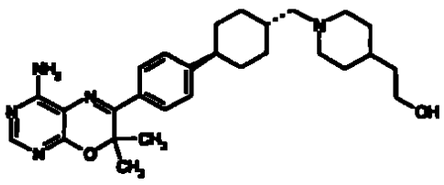
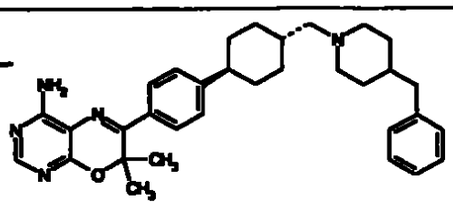
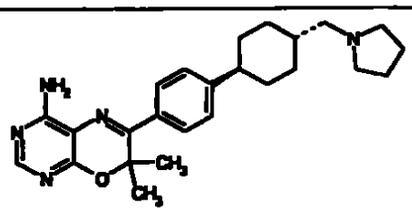
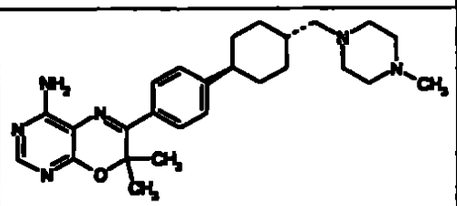
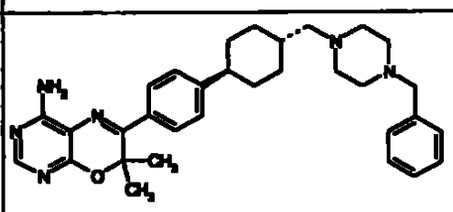
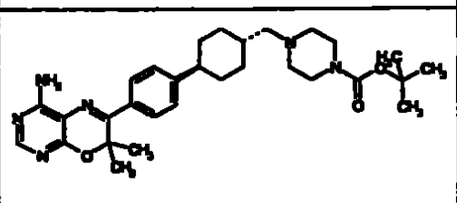
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-191		>250	1.00-1.11(m, 2H), 1.25-1.35(m, 1H), 1.43-1.50(m, 4H), 1.58(s, 6H), 1.78-1.86(m, 4H), 2.22-2.28(m, 2H), 2.24(s, 3H), 6.82(brs, 2H), 7.29(d, 2H, J=9.0Hz), 7.82(d, 2H, J=9.0Hz), 11.99(brs, 1H)	DMSO-d6, 300MHz
2-192		>250	0.99-1.12(m, 2H), 1.22-1.33(m, 1H), 1.42-1.52(m, 4H), 1.58(s, 6H), 1.80-1.84(m, 4H), 2.24(s, 3H), 2.32(t, 2H, J=7.5Hz), 3.23(s, 3H), 6.81(brs, 2H), 7.29(d, 2H, J=9.0Hz), 7.82(d, 2H, J=9.0Hz), 11.66(brs, 1H)	DMSO-d6, 300MHz
2-193		>240	0.96-1.12(m, 2H), 1.17(s, 6H), 1.21-1.30(m, 1H), 1.36-1.49(m, 4H), 1.58(s, 6H), 1.77-1.87(m, 4H), 2.09(t, 2H, J=7.5Hz), 2.24(s, 3H), 2.47-2.58(m, 1H), 3.37(d, 2H, J=6.0Hz), 4.88(t, 1H, J=6.0Hz), 6.80(br, 2H), 7.24(brs, 1H), 7.29(d, 2H, J=9.0Hz), 7.82(d, 2H, J=9.0Hz)	DMSO-d6, 300MHz
2-194		230 - 231	0.99-1.12(m, 2H), 1.25-1.36(m, 1H), 1.37-1.52(m, 4H), 1.58(s, 6H), 1.79-1.87(m, 4H), 2.22(t, 2H, J=7.5Hz), 2.24(s, 3H), 2.49-2.57(m, 1H), 3.17(dd, 1H, J=12.0, 6.0Hz), 3.25(dd, 1H, J=12.0, 6.0Hz), 3.36(dd, 1H, J=12.0, 6.0Hz), 3.57(dd, 1H, J=12.0, 6.0Hz), 3.94-4.01(m, 1H), 4.01-4.06(m, 1H), 4.88(d, 1H, J=6.0Hz), 4.93(d, 1H, J=6.0Hz), 6.81(br, 1H), 7.29(d, 2H, J=9.0Hz), 7.82(d, 2H, J=9.0Hz)	DMSO-d6, 300MHz
2-195		250(deg.)	1.06-1.13(m, 2H), 1.43-1.54(m, 5H), 1.58(s, 6H), 1.84(m, 4H), 2.24(s, 3H), 2.55(d, 2H, J=7.5Hz), 6.83(brs, 2H), 7.29(d, 2H, J=8.3Hz), 7.82(d, 2H, J=8.3Hz).	DMSO-d6, 400MHz
2-196		211(deg.)	1.06-1.13(m, 2H), 1.44-1.54(m, 5H), 1.58(s, 6H), 1.84(m, 4H), 2.24(s, 3H), 2.55(d, 2H, J=7.5Hz), 6.82(brs, 2H), 7.29(d, 2H, J=8.3Hz), 7.82(d, 2H, J=8.3Hz).	DMSO-d6, 300MHz
2-197		250(deg.)	1.04-1.15(m, 2H), 1.36-1.49(m, 5H), 1.58(s, 6H), 1.86(m, 4H), 2.24(m, 2H), 2.54(m, 1H), 2.66(m, 2H), 3.89(s, 3H), 6.82(brs, 2H), 7.29(d, 2H, J=8.3Hz), 7.82(d, 2H, J=8.3Hz).	DMSO-d6, 300MHz

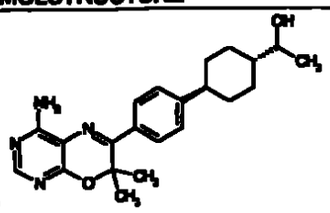
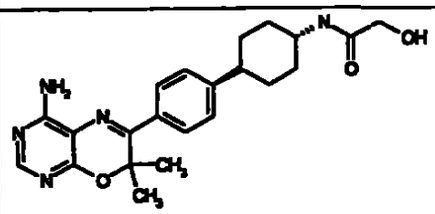
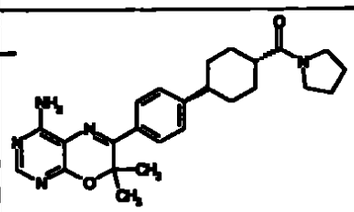
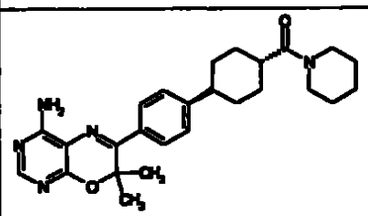
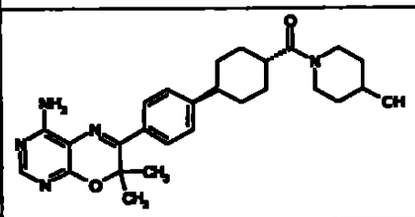
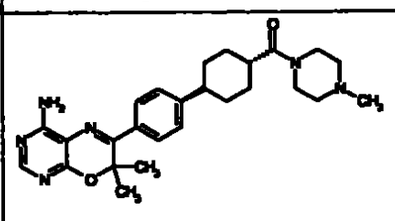
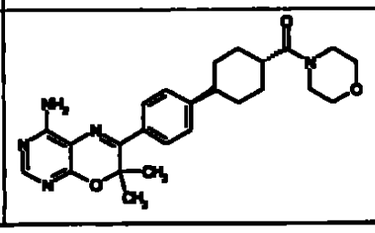
New Ex. No.	MOLSTRUCTURE	m p	NMR(δ)	solvent
2-198		>250	1.04-1.11(m, 2H), 1.39-1.52(m, 5H), 1.58(s, 6H), 1.86(m, 4H), 2.24(s, 3H), 2.64(m, 2H), 3.57(s, 3H), 4.88(t, 1H, J=5.3Hz), 6.83(brs, 2H), 7.29(d, 2H, J=8.3Hz), 7.44(t, 1H, J=5.6Hz), 7.62(d, 2H, J=8.3Hz).	DMSO-d6, 300MHz
2-199		198 - 200	1.10-1.15(m, 2H), 1.43-1.50(m, 3H), 1.89(s, 6H), 1.78(m, 2H), 1.94(m, 4H), 2.47(s, 3H), 2.67(m, 1H), 2.90(m, 2H), 5.74(brs, 2H), 7.25(d, 2H, J=8.3Hz), 7.54(d, 2H, J=8.3Hz).	CDCl3, 300MHz
2-200		>250	1.04-1.19(m, 3H), 1.37-1.52(m, 2H), 1.58(s, 6H), 1.62-1.89(m, 2H), 1.79-1.91(m, 4H), 2.24(s, 3H), 2.47-2.68(m, 1H), 2.93(t, 2H, J=7.5Hz), 6.81(brs, 2H), 7.29(d, 2H, J=9.0Hz), 7.62(d, 2H, J=9.0Hz)	DMSO-d6, 300MHz
2-201		>250	1.03-1.15(m, 2H), 1.27-1.41(m, 1H), 1.39-1.53(m, 4H), 1.58(s, 6H), 1.81-1.87(m, 4H), 2.24(s, 3H), 2.46-2.53(m, 2H), 2.57(br, 1H), 6.81(br, 1H), 7.29(d, 2H, J=9.0Hz), 7.62(d, 2H, J=9.0Hz), 11.96(brs, 1H), 15.76(br, 1H)	DMSO-d6, 300MHz
2-202		>225	1.02-1.18(m, 2H), 1.11(s, 6H), 1.34-1.53(m, 5H), 1.58(s, 6H), 1.69-1.85(m, 4H), 2.24(s, 3H), 2.43-2.53(m, 1H), 6.81(br, 2H), 7.28(d, 2H, J=8.3Hz), 7.61(d, 2H, J=8.3Hz), 12.03(brs, 1H)	DMSO-d6, 300MHz
2-203		235 - 237	1.35-1.55(m, 4H), 1.80(s, 6H), 1.77-1.79(m, 4H), 2.15-2.25(m, 1H), 2.48-2.61(m, 1H), 3.11(q, 2H, J=6.0Hz), 3.39(q, 2H, J=6.0Hz), 4.84(t, 1H, J=6.0Hz), 6.97(br, 2H), 7.31(d, 2H, J=8.4Hz), 7.65(d, 2H, J=8.4Hz), 7.74(t, 1H, J=6.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-204		>250	1.43-1.54(m, 4H), 1.80(s, 6H), 1.81-1.95(m, 4H), 2.10-2.24(m, 1H), 2.49-2.63(m, 1H), 6.70(brs, 1H), 6.85(br, 2H), 7.23(brs, 1H), 7.31(d, 2H, J=8.4Hz), 7.65(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz

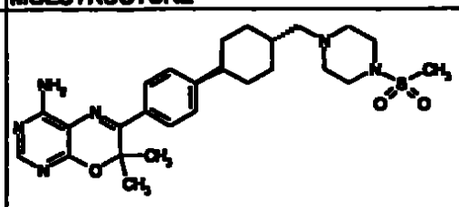
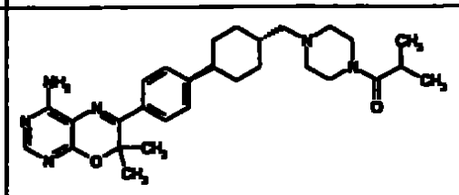
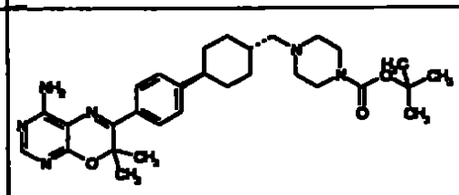
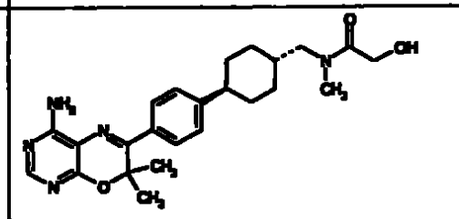
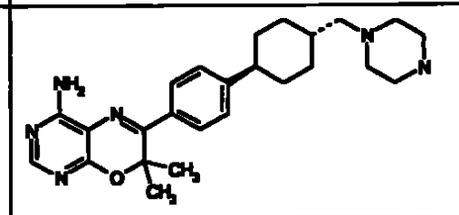
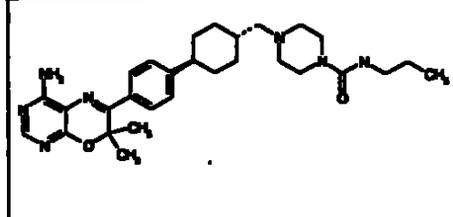
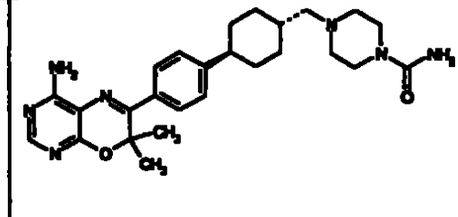
New Ex. No.	MOLSTRUCTURE	m p	NMR(δ)	solvent
2-205		>250	1.41-1.58(m, 4H), 1.61(s, 6H), 1.81-1.91(m, 4H), 2.21-2.31(m, 1H), 2.54-2.60(m, 1H), 3.74(d, 2H, J=5.8Hz), 6.97(br, 2H), 7.31(d, 2H, J=8.1Hz), 7.85(d, 2H, J=8.1Hz), 7.96(s, 1H), 8.04(t, 1H, J=5.8Hz)	DMSO-d6, 400MHz
2-206		>250	1.08(s, 3H), 1.22(s, 3H), 1.41-1.54(m, 4H), 1.80-1.88(m, 2H), 1.96-2.04(m, 2H), 2.22-2.30(m, 1H), 2.47-2.55(m, 1H), 4.11(s, 1H), 5.27(s, 1H), 6.23(s, 2H), 7.25(d, 2H, J=8.1Hz), 7.38(d, 2H, J=8.1Hz), 7.82(s, 1H)	DMSO-d6, 400MHz
2-207		>250	1.45-1.85(m, 7H), 1.60(s, 6H), 1.80-1.95(m, 6H), 2.50-2.78(m, 3H), 3.05-3.28(m, 1H), 3.86-4.30(m, 2H), 6.90(brs, 2H), 7.30(d, 2H, J=9.0Hz), 7.64(d, 2H, J=9.0Hz), 7.95(s, 1H), 12.05(brs, 1H)	DMSO-d6, 300MHz
2-208		193 - 194	1.45-1.85(m, 4H), 1.60(s, 6H), 1.80-1.95(m, 7H), 2.08-2.19(m, 2H), 2.53-2.63(m, 1H), 3.55-3.63(m, 2H), 4.21-4.25(m, 1H), 6.95(brs, 2H), 7.32(d, 2H, J=9.0Hz), 7.68(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-209		>250	1.23-1.36(m, 2H), 1.48-1.57(m, 2H), 1.60(s, 6H), 1.79(s, 3H), 1.83-1.92(m, 4H), 2.53-2.58(m, 1H), 3.55-3.66(m, 1H), 6.94(brs, 2H), 7.33(d, 2H, J=9.0Hz), 7.65(d, 2H, J=9.0Hz), 7.78(d, 1H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-210		>250	1.24-1.48(m, 4H), 1.58(s, 6H), 1.69-1.76(m, 4H), 2.39(s, 3H), 2.41-2.48(m, 1H), 2.98-3.06(m, 1H), 6.93(brs, 2H), 7.27(d, 2H, J=9.0Hz), 7.40(d, 2H, J=9.0Hz), 7.81(d, 2H, J=9.0Hz), 7.85(d, 1H, J=8.0Hz), 7.73(d, 2H, J=9.0Hz), 7.94(s, 1H)	DMSO-d6, 300
2-211		>250	a mixture of 2 conformers; 1.25 and 1.27(s, 3H), 1.42-1.57(m, 4H), 1.61(s, 6H), 1.79-1.91(m, 4H), 2.21-2.30(m, 1H), 2.52-2.63(m, 1H), 4.14-4.25(m, 1H), 6.96(brs, 2H), 7.32(d, 2H, J=9.0Hz), 7.65(d, 2H, J=8.0Hz), 7.96(s, 1H), 8.04(d, 1H, J=8.0Hz)	DMSO-d6, 300MHz

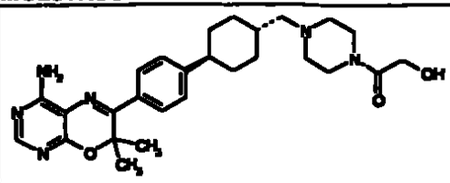
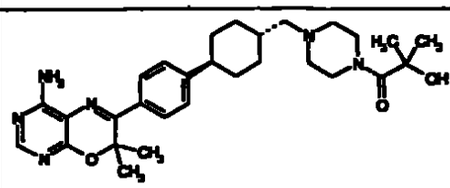
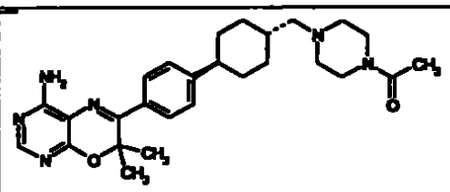
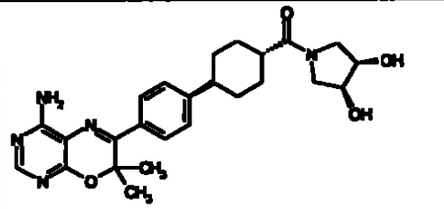
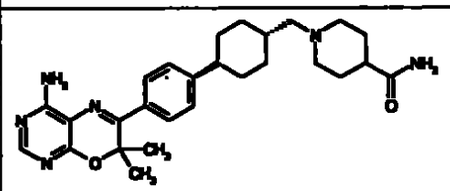
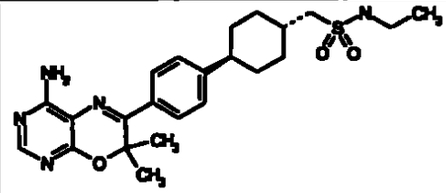
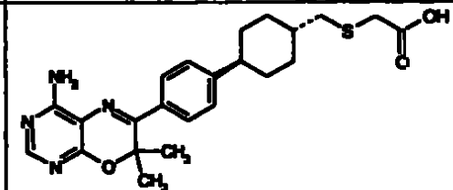
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-212		>250	1.33(s, 6H), 1.42-1.54(m, 4H), 1.60(s, 6H), 1.81-1.88(m, 4H), 2.17-2.25(m, 1H), 2.53-2.59(m, 1H), 6.97(brs, 2H), 7.31(d, 2H, J=9.0Hz), 7.65(d, 2H, J=9.0Hz), 7.90(brs, 1H), 7.98(s, 1H)	DMSO-d6, 300MHz
2-213		>250	1.45-1.57(m, 4H), 1.61(s, 6H), 1.84-1.91(m, 4H), 2.30-2.37(m, 1H), 2.53-2.60(m, 1H), 3.60-3.70(m, 2H), 4.25-4.31(m, 1H), 4.91(brs, 1H), 6.97(brs, 2H), 7.32(d, 2H, J=9.0Hz), 7.66(d, 2H, J=9.0Hz), 7.85(d, 1H, J=9.0Hz), 7.96(s, 1H)	DMSO-d6, 300MHz
2-214		>250	a mixture of 2 conformers: 1.49-1.63(m, 4H), 1.61(s, 6H), 1.80-1.89(m, 4H), 2.81 and 3.09(s, 3H), 3.98 and 4.20(s, 2H), 6.93(brs, 2H), 7.31 and 7.33(d, 2H, J=9.0Hz), 7.65 and 7.68(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-215		>250	1.34-1.44(m, 2H), 1.51-1.58(m, 2H), 1.60(s, 6H), 1.78-1.87(m, 2H), 1.97-2.06(m, 2H), 2.51-2.58(m, 1H), 2.93(s, 3H), 3.19-3.23(m, 1H), 6.90(brs, 2H), 7.03(d, 1H, J=8.0Hz), 7.31(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 400
2-216			1.01-1.10(m, 2H), 1.40-1.49(m, 3H), 1.60(s, 6H), 1.83-1.87(m, 4H), 2.52-2.55(m, 1H), 3.22-3.28(m, 2H), 6.90(brs, 2H), 7.30(d, 2H, J=8.0Hz), 7.63(d, 2H, J=8.0Hz), 7.94(s, 1H)	DMSO-d6, 400
2-217		225 - 227	1.09-1.20(m, 2H), 1.36-1.46(m, 2H), 1.58(s, 6H), 1.78-1.81(m, 5H), 2.52-2.56(m, 1H), 3.48(d, 2H, J=8.0Hz), 6.89(brs, 2H), 7.27(d, 2H, J=12.0Hz), 7.81(d, 2H, J=12.0Hz), 7.82-7.88(m, 4H), 7.92(s, 1H)	DMSO-d6, 400
2-218		212	1.32-1.54(m, 4H), 1.60(s, 6H), 1.81-1.85(m, 2H), 2.05-2.10(m, 2H), 2.53-2.56(m, 1H), 3.09-3.18(m, 1H), 6.46(s, 2H), 6.54(d, 1H, J=9.0Hz), 6.94(brs, 2H), 7.31(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz

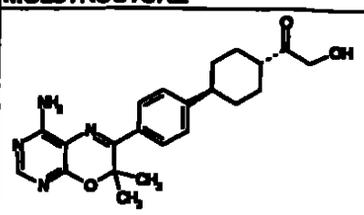
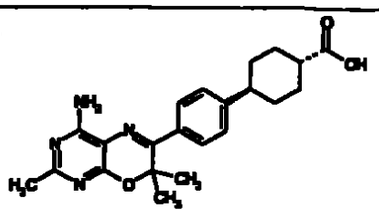
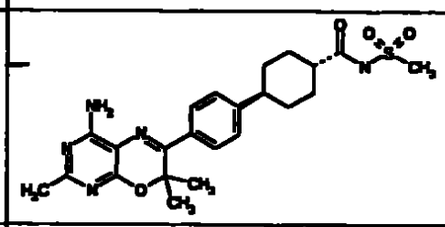
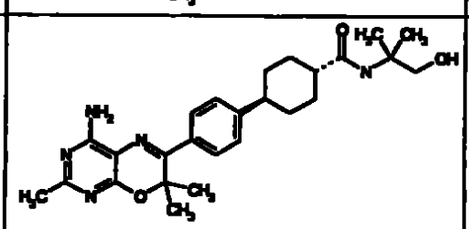
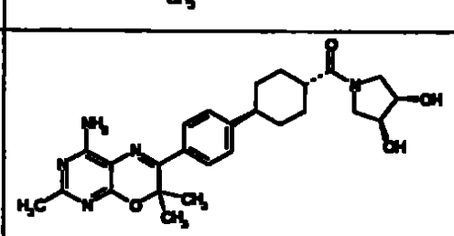
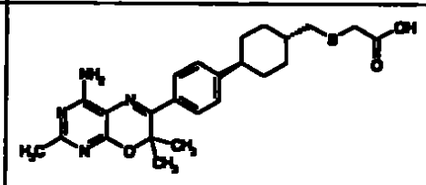
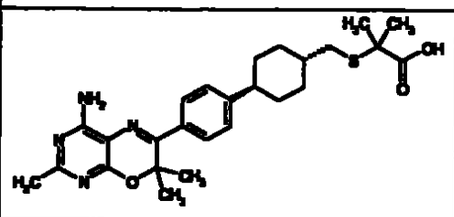
New Ex. No.	MOLSTRUCTURE	m.p	NMR(δ)	solvent
2-219		243-248	1.08(s, 3H), 1.22(s, 3H), 1.44-1.82(m, 4H), 1.89-1.90(m, 4H), 2.45-2.58(m, 1H), 2.63-2.77(m, 1H), 2.81(s, 1.2H), 3.08(s, 1.8H), 4.11(s, 0.6H), 4.16(s, 0.4H), 5.28(s, 1H), 6.20(br, 2H), 7.28(d, 2H, J=8.1Hz), 7.37(d, 2H, J=8.1Hz), 7.61(s, 1H), 12.48(brs, 1H)	DMSO-d6, 400MHz
2-220		>250	1.16-1.29(m, 2H), 1.43-1.56(m, 2H), 1.61(s, 6H), 1.80-2.11(m, 6H), 2.53-2.59(m, 1H), 2.94(d, 2H, J=6.0Hz), 6.79(s, 2H), 6.93(brs, 2H), 7.31(d, 2H, J=9.0Hz), 7.66(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-221		>250	1.08(s, 3H), 1.16-1.27(m, 5H), 1.43-1.52(m, 2H), 1.80-2.08(m, 5H), 2.46-2.49(m, 1H), 2.93(d, 2H, J=6.0Hz), 4.11(brs, 1H), 5.25(brs, 1H), 6.20(brs, 2H), 6.76(s, 2H), 7.24(d, 2H, J=8.0Hz), 7.36(d, 2H, J=8.0Hz), 7.61(s, 1H)	DMSO-d6, 400
2-222		>250	1.07(s, 3H), 1.22(s, 3H), 1.24-1.53(m, 4H), 1.75-2.11(m, 4H), 2.41-2.48(m, 1H), 3.05-3.17(m, 1H), 4.11(brs, 1H), 5.28(brs, 1H), 6.21(brs, 2H), 6.45(brs, 2H), 6.52(d, 1H, J=12.0Hz), 7.24(d, 2H, J=8.0Hz), 7.35(d, 2H, J=8.0Hz), 7.80(s, 1H)	DMSO-d6, 300MHz
2-223			1.00-1.11(m, 5H), 1.22(s, 3H), 1.37-1.48(m, 3H), 1.77-1.85(m, 4H), 2.43-2.48(m, 1H), 3.24-3.27(m, 2H), 4.11(brs, 1H), 4.30-4.32(m, 1H), 5.26(brs, 1H), 6.20(brs, 2H), 7.24(d, 2H, J=8.0Hz), 7.36(d, 2H, J=8.0Hz), 7.61(s, 1H)	DMSO-d6, 400
2-224		169 - 171	0.94-1.08(m, 2H), 1.36-1.80(m, 16H), 1.76-1.93(m, 4H), 2.03-2.13(m, 2H), 2.25-2.35(m, 3H), 2.52-2.56(m, 1H), 6.91(brs, 2H), 7.30(d, 2H, J=12.0Hz), 7.64(d, 2H, J=12.0Hz), 7.94(s, 1H)	DMSO-d6, 400
2-225			0.82-1.08(m, 2H), 1.29-2.15(m, 21H), 2.53-2.58(m, 1H), 2.64-2.73(m, 2H), 3.38-3.48(m, 1H), 4.47-4.51(m, 1H), 6.91(brs, 2H), 7.30(d, 2H, J=9.0Hz), 7.64(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300

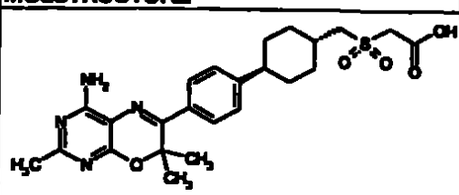
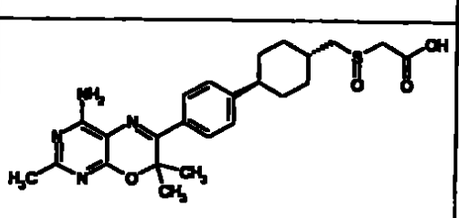
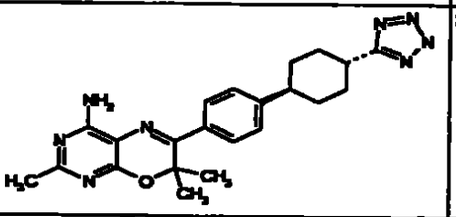
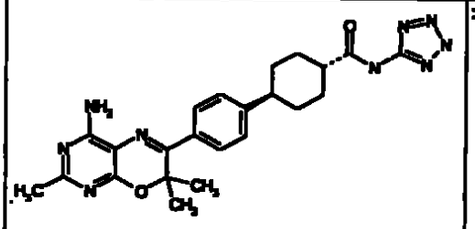
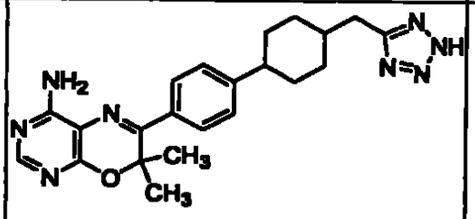
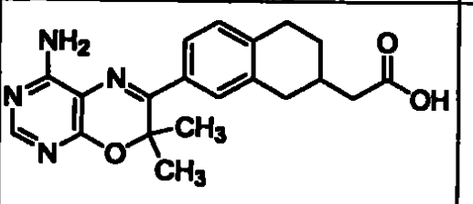
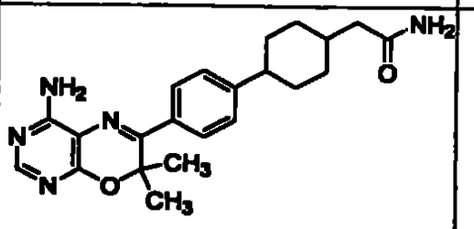
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-228			0.97-1.11(m, 2H), 1.40-1.88(m, 11H), 1.78-2.01(m, 7H), 2.18-2.31(m, 2H), 2.39-2.47(m, 2H), 2.62-2.74(m, 2H), 4.75(brs, 1H), 6.92(brs, 2H), 7.18-7.36(m, 5H), 7.49(d, 2H, J=9.0Hz), 7.85(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-227		198 - 200	0.91-1.89(m, 21H), 1.77-1.94(m, 4H), 2.05-2.16(m, 1H), 2.53-2.61(m, 1H), 2.74-2.89(m, 2H), 3.40-3.46(m, 2H), 4.30(brs, 1H), 6.91(brs, 2H), 7.30(d, 2H, J=9.0Hz), 7.85(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-228		119 - 120	0.91-1.85(m, 19H), 1.75-1.90(m, 6H), 2.11(brs, 1H), 2.55-2.58(m, 1H), 2.72-2.91(m, 2H), 6.91(brs, 2H), 7.15-7.33(m, 7H), 7.84(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-229		160 - 162	0.97-1.11(m, 2H), 1.39-1.97(m, 19H), 2.27-2.83(m, 3H), 3.24(brs, 2H), 6.91(brs, 2H), 7.30(d, 2H, J=8.0Hz), 7.84(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-230			0.91-1.10(m, 2H), 1.37-1.83(m, 11H), 1.78-1.92(m, 5H), 2.08-2.42(m, 10H), 2.52-2.58(m, 1H), 6.91(brs, 2H), 7.30(d, 2H, J=9.0Hz), 7.84(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-231			0.95-1.07(m, 2H), 1.37-1.85(m, 11H), 1.78-1.91(m, 4H), 2.15-2.23(m, 2H), 2.32-2.47(m, 6H), 3.45-3.51(m, 2H), 6.91(brs, 2H), 7.25-7.35(m, 7H), 7.84(d, 2H, J=9.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-232		171 - 172	0.96-1.08(m, 2H), 1.39(s, 9H), 1.41-1.51(m, 2H), 1.80(s, 6H), 1.80-1.91(m, 5H), 2.13(brs, 2H), 2.28-2.32(m, 4H),2.48-2.53(m, 4H), 2.52-2.57(m, 1H), 6.90(brs, 2H), 7.28(d, 2H, J=8.0Hz), 7.82(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz

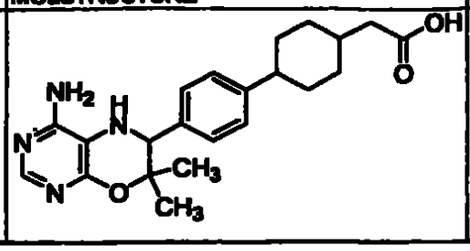
New Ex. No.	MOLSTRUCTURE	mp	NMR(δ)	solvent
2-233		224 - 229	1.08(d, 3H, J=6.0Hz), 1.09-1.31(m, 3H), 1.38-1.52(m, 2H), 1.61(s, 6H), 1.71-1.82(m, 1H), 1.90-1.93(m, 2H), 2.01-2.47(m, 1H), 3.37-3.46(m, 1H), 6.93(br, 2H), 7.30(d, 2H, J=8.4Hz), 7.84(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 400MHz
2-234		226 - 230	1.37-1.67(m, 4H), 1.61(s, 6H), 1.78-1.92(m, 4H), 2.46-2.60(m, 1H), 3.62-3.78(m, 1H), 3.79(s, 2H), 6.93(br, 2H), 7.33(d, 2H, J=8.4Hz), 7.48(d, 1H, J=8.4Hz), 7.85(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-235		201 - 202	1.48-1.68(m, 4H), 1.61(s, 6H), 1.71-1.83(m, 8H), 2.43-2.63(m, 2H), 3.26-3.35(m, 2H), 3.43-3.54(m, 2H), 6.93(br, 2H), 7.31(d, 2H, J=8.4Hz), 7.85(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-236		220 - 224	1.33-1.89(m, 14H), 1.61(s, 6H), 2.51(s, 2H), 3.36(s, 4H), 6.92(br, 2H), 7.31(d, 2H, J=8.1Hz), 7.85(d, 2H, J=8.1Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-237		250 - 252	1.16-1.39(m, 2H), 1.46-1.92(m, 8H), 1.61(s, 6H), 2.51-2.81(m, 2H), 2.87-3.05(m, 1H), 3.12-3.25(m, 1H), 3.52-3.99(m, 4H), 4.64-4.78(m, 1H), 6.93(br, 2H), 7.31(d, 2H, J=8.4Hz), 7.85(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-238		190- 191	1.48-1.85(m, 4H), 1.61(s, 6H), 1.72-1.92(m, 4H), 2.20(s, 3H), 2.22-2.38(m, 4H), 2.51-2.75(m, 2H), 3.41-3.55(m, 4H), 6.93(br, 2H), 7.31(d, 2H, J=8.4Hz), 7.85(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-239		233 - 235	1.47-1.67(m, 4H), 1.57(s, 6H), 1.70-1.92(m, 4H), 2.47-2.77(m, 2H), 3.37-3.65(m, 8H), 6.92(br, 2H), 7.31(d, 2H, J=8.4Hz), 7.85(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz

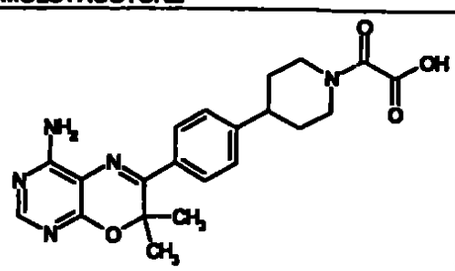
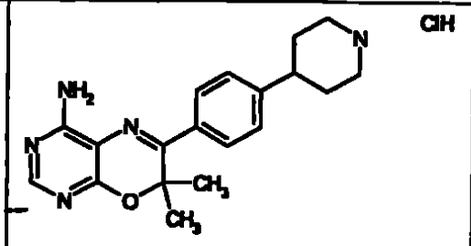
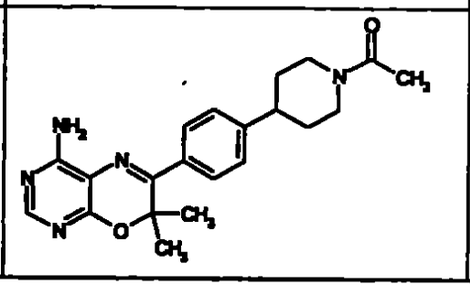
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-240		233 - 235	0.95-1.09(m, 2H), 1.37-1.85(m, 3H), 1.60(s, 6H), 1.77-1.98(m, 4H), 2.19(brd, 2H, J=7.0Hz), 2.39-2.49(m, 4H), 2.50-2.61(m, 1H), 3.07-3.14(m, 4H), 6.91(br, 2H), 7.30(d, 2H, J=8.4Hz), 7.64(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-241		120 - 126	0.98-1.10(m, 2H), 0.99(d, 6H, J=6.6Hz), 1.41-1.85(m, 3H), 1.60(s, 6H), 1.81-1.93(m, 4H), 2.15(brd, 2H, J=7.0Hz), 2.27-2.38(m, 4H), 2.48-2.59(m, 1H), 2.80-2.89(m, 1H), 3.40-3.51(m, 4H), 6.92(br, 2H), 7.30(d, 2H, J=8.4Hz), 7.64(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-242		171 - 172	0.99-1.08(m, 2H), 1.39(s, 9H), 1.41-1.51(m, 2H), 1.60(s, 6H), 1.80-1.91(m, 5H), 2.13(bra, 2H), 2.28-2.32(m, 4H),2.48-2.53(m, 4H), 2.52-2.57(m, 1H), 6.90(bra, 2H), 7.29(d, 2H, J=8.0Hz), 7.62(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-243		208 - 210	a mixture of 2 conformers; 1.02-1.13(m, 2H), 1.38-1.58(m, 2H), 1.59(s, 6H), 1.81-1.91(m, 5H), 2.51(m, 1H), 2.85 and 2.87(s, 3H), 3.08 and 3.20(d, 2H, J=6.8 Hz), 4.06 and 4.07(bra, 2H), 4.30 and 4.35(bra, 1H), 6.91(bra, 2H), 7.27(d, 2H, J=8.3 Hz), 7.61(d, 2H, J=8.3 Hz), 7.92(s, 1H).	DMSO-d6, 400MHz
2-244		208 - 209	0.94-1.05(m, 2H), 1.41-1.50(m, 2H), 1.60(s, 6H), 1.79-1.90(m, 5H), 2.08(d, 2H, J=8.0Hz), 2.23-2.29(m, 4H), 2.69-2.71(m, 4H), 6.92(bra, 2H), 7.28(d, 2H, J=8.0Hz), 7.62(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-245		180 - 182	0.82(t, 3H, J=7.4 Hz), 1.04-1.13(m, 2H), 1.37-1.58(m, 5H), 1.60(s, 6H), 1.80-1.95(m, 4H), 2.01-2.18(m, 2H), 2.19-2.39(m, 4H), 2.51(m, 1H), 2.95(q, 2H, J=7.4 Hz), 3.20-3.28(m, 4H), 6.40(bra, 1H), 6.91(bra, 2H), 7.28(d, 2H, J=8.3 Hz), 7.62(d, 2H, J=8.3 Hz), 7.93(s, 1H).	DMSO-d6, 400MHz
2-246		158 - 160	1.04-1.13(m, 2H), 1.37-1.58(m, 3H), 1.59(s, 6H), 1.80-1.95(m, 4H), 2.01-2.18(m, 2H), 2.19-2.39(m, 4H), 2.51(m, 1H), 3.20-3.28(m, 4H), 5.89(bra, 2H), 6.91(bra, 2H), 7.27(d, 2H, J=8.3 Hz), 7.61(d, 2H, J=8.3 Hz), 7.92(s, 1H).	DMSO-d6, 400MHz

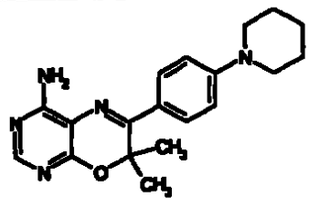
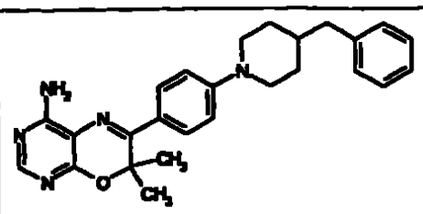
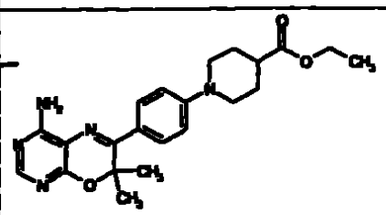
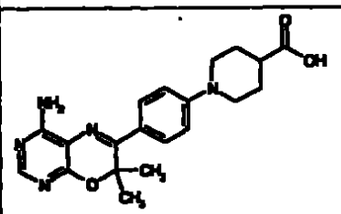
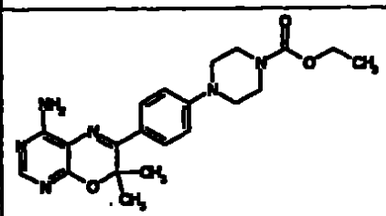
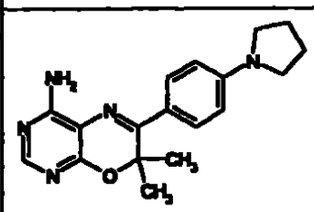
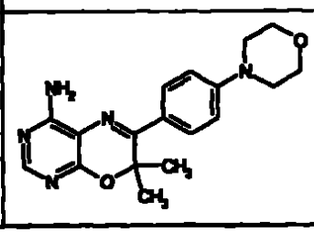
New Ex. No.	MOLSTRUCTURE	m p	NMR(δ)	solvent
2-247		205 - 206	0.99-1.07(m, 2H), 1.43-1.51(m, 2H), 1.80(s, 6H), 1.80-1.92(m, 5H), 2.14(d, 2H, J=8.0Hz), 2.28-2.38(m, 4H), 2.52-2.58(m, 1H), 3.43-3.48(m, 4H), 4.07(d, 2H, J=6.0Hz), 4.33(t, 1H, J=6.0Hz), 6.93(brs, 2H), 7.28(d, 2H, J=8.0Hz), 7.63(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-248		207 - 208	1.00-1.04(m, 2H), 1.30(s, 6H), 1.40-1.52(m, 2H), 1.80(s, 6H), 1.79-1.93(m, 5H), 2.13(d, 2H, J=8.0Hz), 2.30-2.35(m, 4H), 2.53-2.58(m, 1H), 3.79-3.97(m, 4H), 6.92(brs, 2H), 7.28(d, 2H, J=8.0Hz), 7.63(d, 2H, J=12.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-249		202 - 203	0.97-1.06(m, 2H), 1.43-1.52(m, 2H), 1.80(s, 6H), 1.81-1.92(m, 5H), 1.98(s, 3H), 2.14(d, 2H, J=8.0Hz), 2.28-2.38(m, 4H), 2.52-2.58(m, 1H), 3.38-3.45(m, 4H), 6.93(brs, 2H), 7.28(d, 2H, J=8.0Hz), 7.63(d, 2H, J=12.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-250		220 - 240	1.43-1.69(m, 4H), 1.81(s, 6H), 1.73-1.92(m, 4H), 2.36-2.84(m, 2H), 3.13-3.41(m, 3H), 3.65(dd, 1H, J=5.9, 9.9Hz), 3.96-4.11(m, 2H), 4.85(br, 1H), 4.92(br, 1H), 6.93(br, 2H), 7.32(d, 2H, J=8.4Hz), 7.85(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-251		159 - 164	.09(m, 2H), 1.39-1.72(m, 8H), 1.80(s, 6H), 1.77-1.93(m, 6H), 1.97-2.16(m, 2H), 2.45-2.81(m, 1H), 2.76-2.86(m, 1H), 6.67(br, 1H), 6.91(br, 2H), 7.17(br, 1H), 7.30(d, 2H, J=8.1Hz), 7.84(d, 2H, J=8.1Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-252		209 - 211	1.04(t, 3H, J=7.4 Hz), 1.20-1.29(m, 2H), 1.48-1.58(m, 2H), 1.80(s, 6H), 1.80-1.95(m, 4H), 2.01-2.07(m, 2H), 2.51(m, 1H), 2.92-3.01(m, 4H), 6.90(brs, 1H), 7.96(brt, 1H, J=5.6 Hz), 7.29(d, 2H, J=8.3 Hz), 7.83(d, 2H, J=8.3 Hz), 7.94(s, 1H).	DMSO-d6, 400MHz
2-253		248(dec.)	1.03-1.17(m, 2H), 1.38-1.84(m, 8H), 1.78-1.96(m, 4H), 2.55(d, 2H, J=9.0Hz), 3.22(s, 2H), 3.30(s, 2H), 6.92(brs, 2H), 7.30(d, 2H, J=8.0Hz), 7.84(d, 2H, J=8.0Hz), 7.95(s, 1H), 12.40(brs, 1H)	DMSO-d6, 300

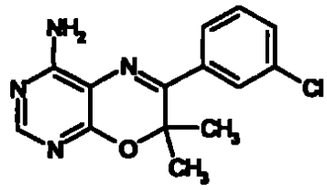
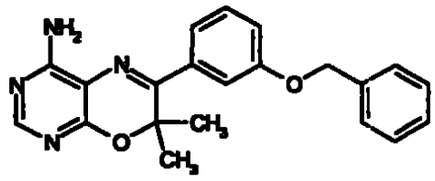
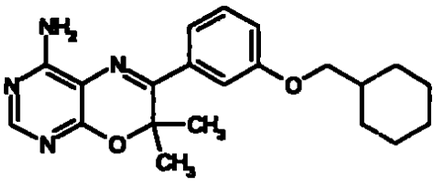
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-254		213 - 214	1.39-1.52(m, 4H), 1.60(s, 6H), 1.85-1.93(m, 4H), 2.52-2.68(m, 2H), 4.18(bra, 2H), 4.97(bra, 1H), 6.93(bra, 2H), 7.29(d, 2H, J=8.0Hz), 7.63(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-255		>250	1.44-1.53(m, 4H), 1.58(s, 6H), 1.82-1.89(m, 2H), 1.98-2.03(m, 2H), 2.24(s, 3H), 2.28(bra, 1H), 6.84(bra, 2H), 7.30(d, 2H, J=9.0Hz), 7.63(d, 2H, J=9.0Hz), 12.05(bra, 1H)	DMSO-d6, 300MHz
2-256		172 - 175	1.42-1.55(m, 4H), 1.59(s, 6H), 1.84-1.97(m, 4H), 2.24(s, 3H), 2.26-2.28(m, 1H), 2.73(bra, 1H), 3.23(bra, 3H), 7.30(d, 2H, J=8.0Hz), 7.63(d, 2H, J=8.0Hz), 11.87(bra, 1H)	DMSO-d6, 300MHz
2-257		220 - 225	1.18(s, 6H), 1.36-1.56(m, 4H), 1.58(s, 6H), 1.79-1.87(m, 4H), 2.15-2.22(m, 1H), 2.24(s, 3H), 2.55-2.59(m, 1H), 3.37(d, 2H, J=6.0Hz), 4.90(t, 1H, J=6.0Hz), 6.82(br, 2H), 7.18(bra, 1H), 7.29(d, 2H, J=9.0Hz), 7.63(d, 2H, J=9.0Hz)	DMSO-d6, 300MHz
2-258		>250	1.44-1.61(m, 4H), 1.58(s, 6H), 1.75-1.88(m, 4H), 2.25(s, 3H), 2.41-2.51(m, 2H), 2.54-2.62(m, 1H), 3.18(dd, 1H, J=12.0, 6.0Hz), 3.37(dd, 1H, J=12.0, 6.0Hz), 3.85(dd, 1H, J=9.0, 6.0Hz), 3.96-4.02(m, 1H), 4.02-4.10(m, 1H), 4.87(d, 1H, J=6.0Hz), 4.95(d, 1H, J=6.0Hz), 6.83(br, 1H), 7.31(d, 2H, J=9.0Hz), 7.63(d, 2H, J=9.0Hz)	DMSO-d6, 300MHz
2-259		271 - 277	1.05- 1.20 (m, 2 H), 1.36- 1.62 (m, 3 H), 1.58 (s, 6 H), 1.77- 1.98 (m, 4 H), 2.24 (s, 3 H), 2.47- 2.59 (m, 1 H), 2.54 (d, J = 6.0 Hz, 2 H), 3.31 (s, 2 H), 6.81 (br s, 2 H), 7.29 (d, J = 9.0 Hz, 2 H), 7.62 (d, J = 9.0 Hz, 2 H), 12.48 (s, 1 H).	DMSO-d6, 300 MHz
2-260		235-239	1.01- 1.21 (m, 2 H), 1.32- 1.54 (m, 3 H), 1.41 (s, 6 H), 1.58 (s, 6 H), 1.77- 1.97 (m, 4 H), 2.24 (s, 3 H), 2.43- 2.61 (m, 3 H), 6.83 (br s, 2 H), 7.28 (d, J = 8.2 Hz, 2 H), 7.61 (d, J = 8.2 Hz, 2 H), 12.49 (br s, 1 H).	DMSO-d6, 300 MHz

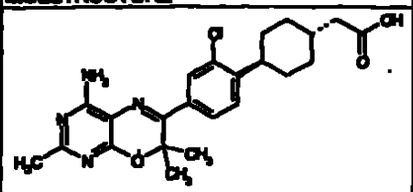
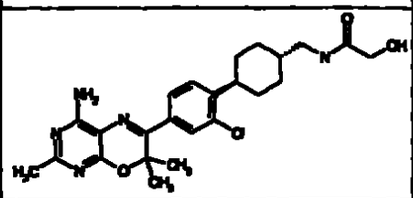
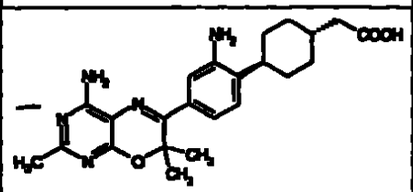
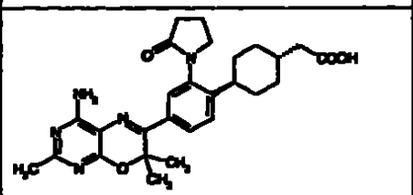
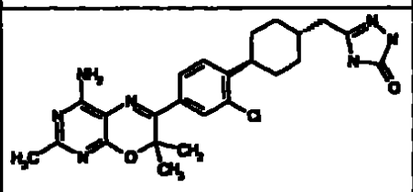
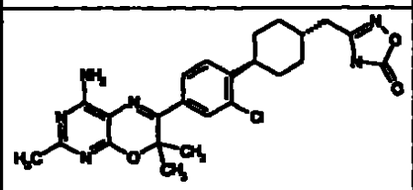
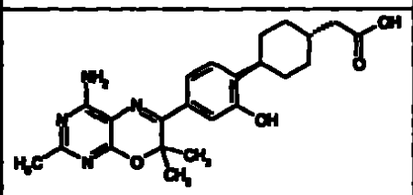
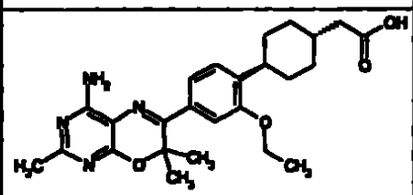
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
2-261		225-227	1.17- 1.38 (m, 2 H), 1.44- 1.66 (m, 2 H), 1.58 (s, 6 H), 1.77- 1.88 (m, 2 H), 1.96- 2.16 (m, 3 H), 2.25 (s, 3 H), 2.45- 2.62 (m, 1 H), 3.27 (d, J = 6.0 Hz, 2 H), 4.26 (s, 2 H), 6.81 (br s, 2 H), 7.30 (d, J = 8.2 Hz, 2 H), 7.62 (d, J = 8.2 Hz, 2 H), 13.36 (br s, 1 H).	DMSO-d6, 300 MHz
2-262		>166	1.18- 1.37 (m, 2 H), 1.48- 1.64 (m, 2 H), 1.58 (s, 6 H), 1.79- 1.94 (m, 4 H), 1.96- 2.09 (m, 1 H), 2.24 (s, 3 H), 2.44- 2.61 (m, 1 H), 2.64- 2.74 (m, 1 H), 2.81- 2.89 (m, 1 H), 3.86 (d, J = 14.1 Hz, 1 H), 3.92 (d, J = 14.1 Hz, 1 H), 6.80 (br s, 2 H), 7.29 (d, J = 8.4 Hz, 2 H), 7.61 (d, J = 8.4 Hz, 2 H), 13.08 (s, 1 H).	DMSO-d6, 400 MHz
2-263		>250	1.59(s, 6H), 1.61-1.75(m, 4H), 1.89-1.99(m, 2H), 2.10-2.21(m, 2H), 2.25(s, 3H), 2.87(br, 1H), 3.09(br, 1H), 6.83(br, 2H), 7.35(d, 2H, J=8.0Hz), 7.65(d, 2H, J=8.0Hz), 16.07(bra, 1H)	DMSO-d6, 300MHz
2-264		>250	1.44-1.69(m, 4H), 1.59(s, 6H), 1.89-1.94(m, 2H), 2.00-2.04(m, 2H), 2.25(s, 3H), 2.55-2.66(m, 2H), 3.16-3.18(m, 2H), 6.83(br, 1H), 7.33(d, 2H, J=9.0Hz), 7.64(d, 2H, J=9.0Hz), 11.99(br, 1H)	DMSO-d6, 300MHz
2-265				
2-266				
2-267				

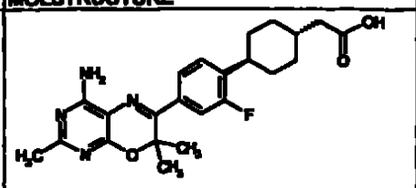
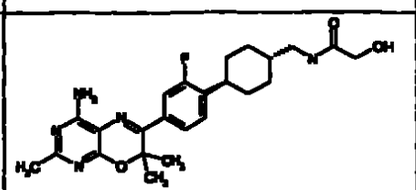
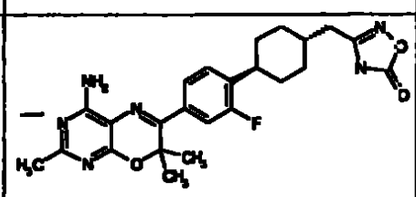
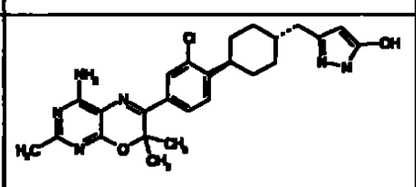
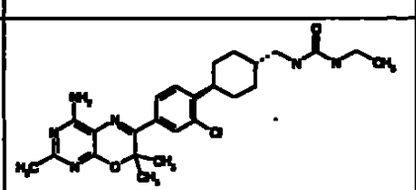
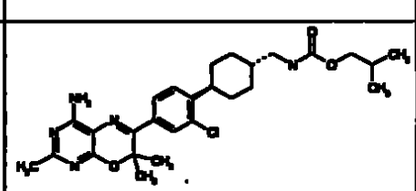
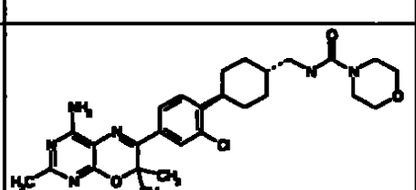
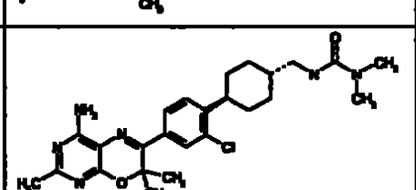
New Ex. No.	MOLSTRUCTURE	m p	NMR(δ)	solvent
2-288				

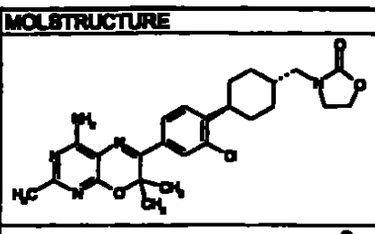
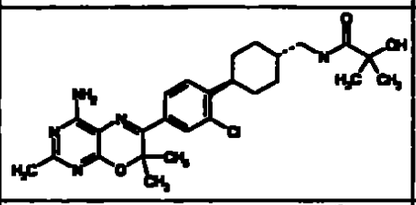
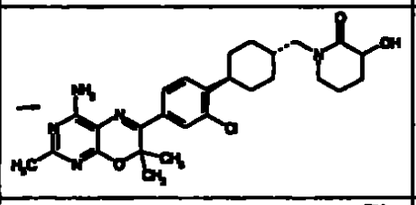
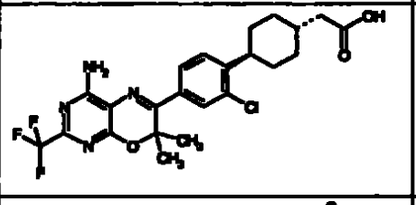
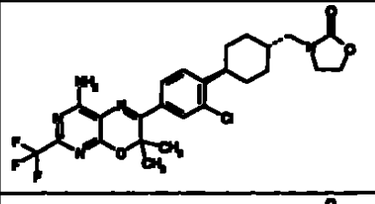
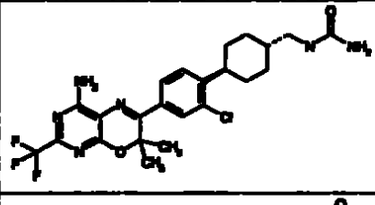
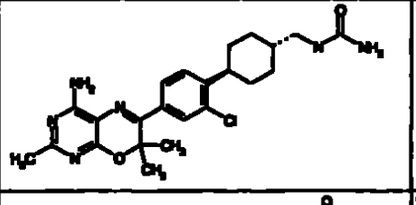
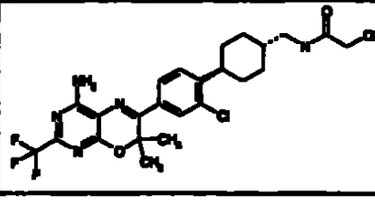
New Ex. No.	MOLSTRUCTURE	m p	NMR(δ)	solvent
3		188 - 190	1.46-1.65(m, 2H), 1.60(s, 6H), 1.81-1.94(m, 2H), 2.73-2.96(m, 2H), 3.22-3.34(m, 1H), 3.63-3.70(m, 1H), 4.33-4.44(m, 1H), 7.00(br, 2H), 7.33(d, 2H, J=8.4Hz), 7.67(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
3-2			1.63(s, 6H), 1.76-2.02(m, 4H), 2.83-3.11(m, 3H), 3.32-3.47(m, 2H), 7.24(br, 2H), 7.32(d, 2H, J=8.1Hz), 7.73(d, 2H, J=8.1Hz), 8.04(s, 1H), 8.69(br, 1H)	DMSO-d6, 300MHz
3-3		232 - 237	1.39-1.54(m, 2H), 1.60(s, 6H), 1.73-1.84(m, 2H), 2.04(s, 3H), 2.54-2.64(m, 1H), 2.77-2.90(m, 1H), 3.07-3.20(m, 1H), 3.87-3.98(m, 1H), 4.49-4.60(m, 1H), 6.95(br, 2H), 7.33(d, 2H, J=8.4Hz), 7.66(d, 2H, J=8.4Hz), 7.96(s, 1H)	DMSO-d6, 300MHz

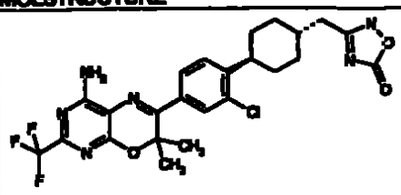
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
4		191 - 193	1.58-1.62(m, 6H), 1.62(s, 6H), 3.26(brs, 4H), 6.79(brs, 2H), 7.29(d, 2H, J=9.0 Hz), 7.83(d, 2H, J=9.0 Hz), 7.91(s, 1H).	DMSO-d6, 400MHz
4-2			1.21-1.30(m, 2H), 1.62(s, 6H), 1.61-1.80(m, 3H), 2.54(d, 2H, J=7.0 Hz), 2.73(brt, 2H, J=12.8 Hz), 3.83(brd, 2H, J=12.8 Hz), 6.79(brs, 2H), 6.91(d, 2H, J=9.0 Hz), 7.17-7.31(m, 5H), 7.82(d, 2H, J=9.0 Hz), 7.91(s, 1H).	DMSO-d6, 400MHz
4-3		176 - 177	1.19(t, 3H, J=6.0Hz), 1.57-1.69(m, 6H), 1.85-1.92(m, 2H), 2.54-2.61(m, 1H), 2.86-2.95(m, 2H), 3.76-3.83(m, 2H), 4.09(q, 2H, J=7.0Hz), 6.87(brs, 2H), 6.96(d, 2H, J=9.0Hz), 7.85(d, 2H, J=6.0Hz), 7.92(s, 1H)	DMSO-d6, 300
4-4		>240	1.57-1.66(m, 6H), 1.87-1.92(m, 2H), 2.45-2.47(m, 1H), 2.87-2.93(m, 2H), 3.76-3.80(m, 2H), 6.82(brs, 2H), 6.94(d, 2H, J=8.0Hz), 7.84(d, 2H, J=8.0Hz), 7.91(s, 1H)	DMSO-d6, 400
4-5		174 - 175	1.21(t, 3H, J=6.0Hz), 1.62(s, 6H), 3.25-3.27(m, 2H), 3.50-3.53(m, 2H), 4.08(q, 2H, J=6.7Hz), 6.83(brs, 2H), 6.97(d, 2H, J=12.0Hz), 7.86(d, 2H, J=8.0Hz), 7.92(s, 1H)	DMSO-d6, 400
4-6		191 - 196	1.63(s, 6H), 1.96-1.99(m, 4H), 3.25-3.31(m, 4H), 6.55(d, 2H, J=8.8Hz), 6.77(br, 2H), 7.85(d, 2H, J=8.8Hz), 7.90(s, 1H)	DMSO-d6, 400MHz
4-7		214 - 219	1.62(s, 6H), 3.22(t, 4H, J=4.8Hz), 3.76(t, 4H, J=4.8Hz), 6.83(br, 2H), 6.96(d, 2H, J=8.4Hz), 7.87(d, 2H, J=8.4Hz), 7.92(s, 1H)	DMSO-d6, 400MHz

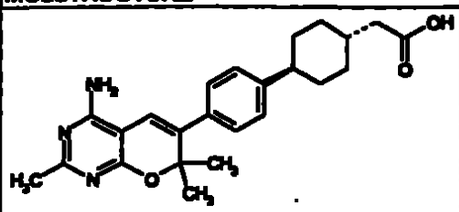
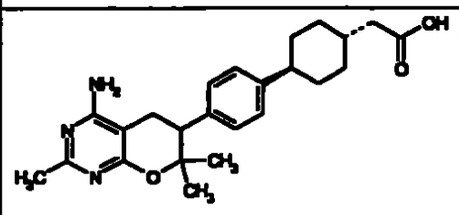
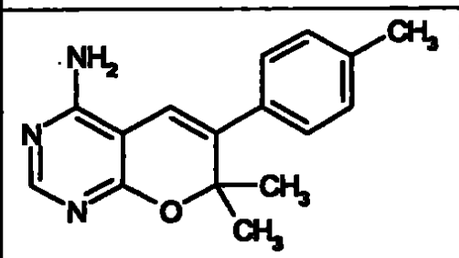
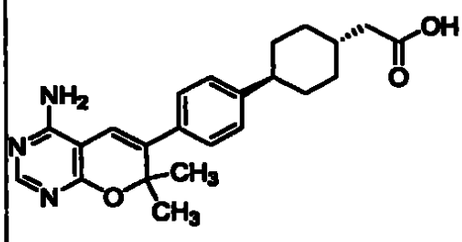
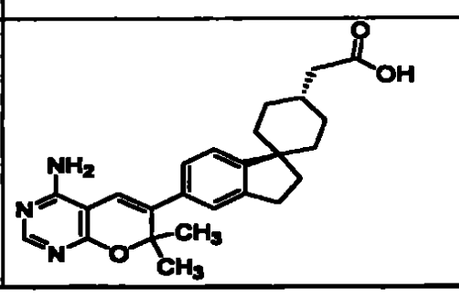
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
5		117 - 133	1.60(s, 6H), 7.01(br, 2H), 7.48(t, 1H, J=8.1Hz), 7.55(ddd, 1H, J=1.0, 2.0, 1.0Hz), 7.67(dt, 1H, J=8.1, 1.0Hz), 7.76(t, 1H, J=2.0Hz), 7.97(s, 1H)	DMSO-d6, 400MHz
5-2		130 - 131	1.58(s, 6H), 5.20(s, 2H), 6.93(br, 2H), 7.15(d, 1H, J=8.3Hz), 7.25-7.49(m, 8H), 7.97(s, 1H)	DMSO-d6, 400MHz
5-3		151 - 152	1.02-1.33(m, 5H), 1.60(s, 6H), 1.65-1.86(m, 6H), 3.85(d, 2H, J=6.2Hz), 6.94(br, 2H), 7.05(dd, 1H, J=2.5, 8.0Hz), 7.17(d, 1H, J=2.5Hz), 7.23(d, 1H, J=8.0Hz), 7.35(t, 1H, J=8.0Hz), 7.97(s, 1H)	DMSO-d6, 400MHz

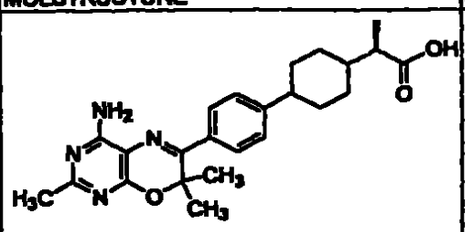
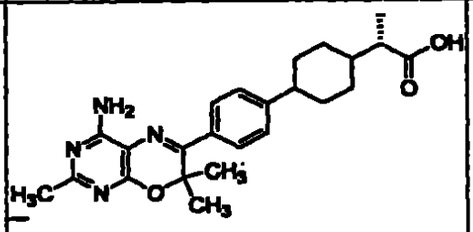
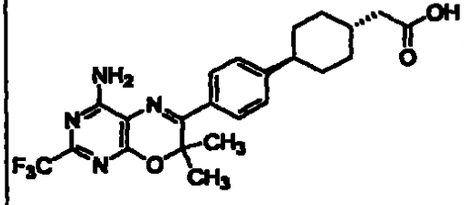
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
6		>230	1.09-1.22(m, 2H), 1.41-1.56(m, 2H), 1.58(s, 6H), 1.70-1.91(m, 6H), 2.18(d, 2H, d=6.7 Hz), 2.24(s, 3H), 2.92(m, 1H), 6.91(bra, 2H), 7.42(d, 1H, J=8.1 Hz), 7.63(dd, 1H, J=8.1, 1.8 Hz), 7.72(d, 1H, J=1.8 Hz), 12.10(bra, 1H).	DMSO-d6, 400MHz
6-2		229 - 232	0.86- 1.16 (m, 2 H), 1.34- 1.84 (m, 3 H), 1.58 (s, 6 H), 1.76- 1.89 (m, 4 H), 2.24 (s, 3 H), 2.83- 2.95 (m, 1 H), 3.02 (t, J = 6.0 Hz, 1 H), 3.81 (s, 2 H), 5.42 (br s, 1 H), 6.91 (br s, 2 H), 7.41 (d, J = 8.3 Hz, 1 H), 7.63 (d, J = 8.3 Hz, 1 H), 7.65- 7.72 (m, 1 H), 7.73 (s, 1 H).	DMSO-d6, 300 MHz
6-3		280(deg.)	1.15-1.42(m, 5H), 1.58(s, 6H), 1.80(m, 4H), 2.23(s, 3H), 2.13(d, 2H, J=6.8Hz), 4.97(bra, 2H), 6.75(bra, 2H), 6.82(dd, 1H, J=8.3Hz, 1.9Hz), 6.93(d, 1H, J=1.9Hz), 7.01(d, 1H, J=8.3Hz).	DMSO-d6, 300MHz
6-4		177(deg.)	1.01-1.09(m, 2H), 1.45-1.56(m, 3H), 1.59(s, 6H), 1.70-1.83(m, 6H), 2.13-2.19(m, 4H), 2.25(s, 3H), 2.41-2.48(m, 2H), 3.63-3.69(m, 2H), 6.87(bra, 2H), 7.42(d, 1H, J=8.3Hz), 7.51(d, 1H, J=1.9Hz), 7.62(dd, 1H, J=8.3, 1.9Hz).	DMSO-d6, 300MHz
6-5		>300	1.15- 1.25 (m, 2 H), 1.37- 1.57 (m, 2 H), 1.58 (s, 6 H), 1.85- 1.94 (m, 5 H), 2.24 (s, 3 H), 2.31 (d, J = 6.8 Hz, 2 H), 2.85- 3.01 (m, 1 H), 6.90 (s, 2 H), 7.41 (d, J = 8.3 Hz, 1 H), 7.63 (dd, J = 1.9, 8.3 Hz, 1 H), 7.73 (d, J = 1.9 Hz, 1 H), 11.07 (s, 1 H), 11.17 (s, 1 H).	DMSO-d6, 300 MHz
6-6		>282	1.13- 1.32 (m, 2 H), 1.39- 1.57 (m, 2 H), 1.58 (s, 6 H), 1.70- 1.96 (m, 5 H), 2.25 (s, 3 H), 2.45 (d, J = 6.8 Hz, 2 H), 2.87- 3.01 (m, 1 H), 6.91 (s, 2 H), 7.42 (d, J = 8.3 Hz, 1 H), 7.64 (dd, J = 1.9, 8.3 Hz, 1 H), 7.74 (d, J = 1.9 Hz, 1 H), 12.17 (s, 1 H).	DMSO-d6, 300 MHz
6-7		>280	1.02- 1.20 (m, 2 H), 1.33- 1.53 (m, 2 H), 1.58 (s, 6 H), 1.85- 1.89 (m, 5 H), 2.14 (d, J = 6.8 Hz, 2 H), 2.24 (s, 3 H), 2.75- 2.89 (m, 1 H), 6.77 (br s, 1 H), 7.07 (d, J = 7.9 Hz, 1 H), 7.08 (s, 1 H), 7.15 (d, J = 7.9 Hz, 1 H), 9.45 (s, 1 H), 11.99 (s, 1 H).	DMSO-d6, 300 MHz
6-8		224-228	1.02- 1.21 (m, 2 H), 1.31- 1.60 (m, 2 H), 1.35 (t, J = 6.9 Hz, 3 H), 1.58 (s, 6 H), 1.86- 1.89 (m, 5 H), 2.15 (d, J = 6.8 Hz, 2 H), 2.25 (s, 3 H), 2.78- 2.83 (m, 1 H), 4.10 (q, J = 6.9 Hz, 2 H), 6.83 (br s, 2 H), 7.17- 7.29 (m, 3 H), 11.96 (s, 1 H).	DMSO-d6, 300 MHz

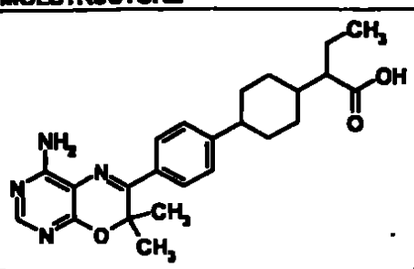
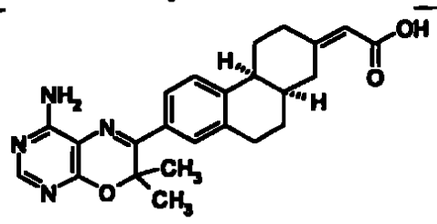
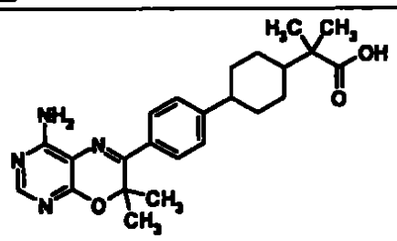
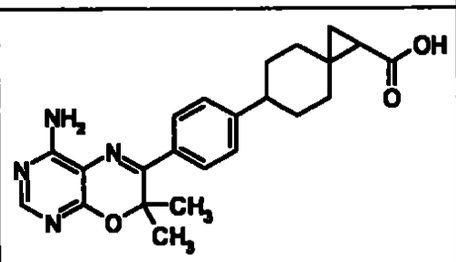
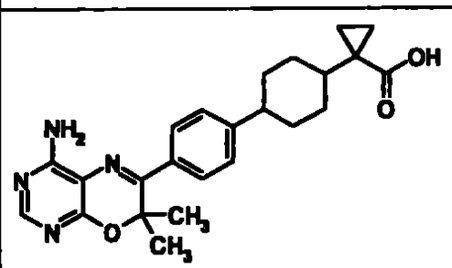
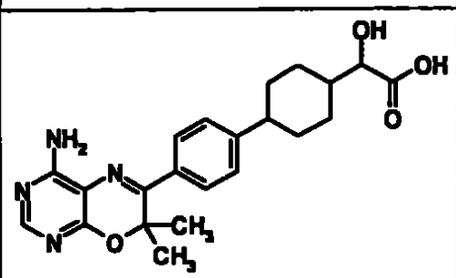
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
6-9		>269	1.07- 1.23 (m, 2 H), 1.44- 1.83 (m, 2 H), 1.59 (s, 6 H), 1.71- 1.90 (m, 5 H), 2.16 (d, J = 6.8 Hz, 2 H), 2.24 (s, 3 H), 2.70- 2.88 (m, 1 H), 6.88 (br s, 2 H), 7.34- 7.42 (m, 1 H), 7.48- 7.55 (m, 2 H), 12.02 (s, 1 H).	DMSO-d6, 300 MHz
6-10		212 - 214	1.01-1.14(m, 2H), 1.42-1.57(m, 3H), 1.59(s, 6H), 1.81(m, 4H), 2.24(s, 3H), 2.80(m, 1H), 3.02(m, 2H), 3.81(d, 2H, J=6.0Hz), 5.1(t, 1H, J=6.0Hz), 6.88(brs, 2H), 7.34-7.40(m, 1H), 7.48-7.54(m, 2H), 7.67-7.71(m, 1H).	DMSO-d6, 300MHz
6-11		>282	1.10- 1.31 (m, 2 H), 1.42- 1.84 (m, 2 H), 1.59 (s, 6 H), 1.67- 1.89 (m, 5 H), 2.24 (s, 3 H), 2.44 (d, J = 6.8 Hz, 2 H), 2.75- 2.88 (m, 1 H), 6.89 (br s, 1 H), 7.33- 7.42 (m, 1 H), 7.47- 7.56 (m, 2 H), 12.16 (s, 1 H).	DMSO-d6, 300 MHz
6-12		171 - 173	1.03-1.19(m, 2H), 1.34-1.51(m, 2H), 1.58(s, 6H), 1.72-1.85(m, 4H), 2.24(s, 3H), 2.39(d, 2H, d=6.7 Hz), 2.92(m, 1H), 5.23(s, 1H), 6.90(brs, 2H), 7.40(d, 1H, J=8.1 Hz), 7.62(d, 1H, J=8.1Hz), 7.72(s, 1H), 9.20(brs, 1H), 11.20(brs, 1H).	DMSO-d6, 400MHz
6-13		>250	1.09(t, 3H, J=7.4 Hz), 1.03-1.16(m, 2H), 1.34-1.54(m, 2H), 1.58(s, 6H), 1.76-1.89(m, 4H), 2.25(s, 3H), 2.83-3.08(m, 5H), 5.70(t, 1H, J=5.8 Hz), 5.85(t, 1H, J=5.8 Hz), 6.90(brs, 2H), 7.43(d, 1H, J=8.1 Hz), 7.64(d, 1H, J=8.1Hz), 7.73(s, 1H).	DMSO-d6, 300MHz
6-14		205 - 209	0.88(d, 6H, J=6.0Hz), 1.01-1.13(m, 2H), 1.37-1.52(m, 3H), 1.58(s, 6H), 1.77-1.87(m, 5H), 2.25(s, 3H), 2.89(t, 2H, J=6.0Hz), 2.88-2.95(m, 1H), 3.73(d, 2H, J=6.0Hz), 6.90(br, 2H), 7.13(br, 1H), 7.42(d, 1H, J=9.0Hz), 7.63(dd, 1H, J=9.0, 3.0Hz), 7.73(d, 1H, J=3.0Hz)	DMSO-d6, 300MHz
6-15		225 - 228	1.00-1.11(m, 2H), 1.36-1.51(m, 3H), 1.58(s, 6H), 1.78-1.86(m, 4H), 2.24(s, 3H), 2.92-2.96(m, 2H), 3.24-3.27(m, 4H), 3.52-3.55(m, 4H), 6.53(t, 1H, J=6.0Hz), 6.90(br, 1H), 7.42(d, 1H, J=9.0Hz), 7.63(dd, 1H, J=9.0, 3.0Hz), 7.73(d, 1H, J=3.0Hz)	DMSO-d6, 300MHz
6-16		>250	0.98-1.10(m, 2H), 1.36-1.52(m, 3H), 1.58(s, 6H), 1.81-1.85(m, 4H), 2.25(s, 3H), 2.78(s, 6H), 2.89-2.94(m, 3H), 6.25(t, 1H, J=6.0Hz), 6.89(br, 2H), 7.42(d, 1H, J=9.0Hz), 7.63(dd, 1H, J=9.0, 3.0Hz), 7.73(d, 1H, J=3.0Hz)	DMSO-d6, 300MHz

New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
6-17		>250	1.07-1.19(m, 2H), 1.45-1.54(m, 2H), 1.59(s, 6H), 1.64-1.74(m, 1H), 1.80-1.87(m, 4H), 2.25(s, 3H), 2.91-3.00(m, 1H), 3.05(d, 2H, J=6.0Hz), 3.56(t, 2H, J=6.0Hz), 4.27(t, 2H, J=6.0Hz), 6.90(br, 2H), 7.42(d, 1H, J=6.0Hz), 7.64(dd, 1H, J=6.0, 3.0Hz), 7.74(d, 1H, J=3.0Hz)	DMSO-d6, 300MHz
6-18		>250	0.99-1.16(m, 2H), 1.25(s, 6H), 1.35-1.53(m, 3H), 1.58(s, 6H), 1.77-1.86(m, 4H), 2.24(s, 3H), 2.86-2.96(m, 1H), 2.99(t, 2H, J=6.0Hz), 5.32(s, 1H), 6.89(br, 2H), 7.42(d, 1H, J=8.3Hz), 7.57-7.66(m, 2H), 7.73(d, 1H, J=1.5Hz)	DMSO-d6, 300MHz
6-19		225 - 228	1.05-1.19(m, 2H), 1.37-1.51(m, 2H), 1.58(s, 6H), 1.60-1.66(m, 1H), 1.71-1.87(m, 6H), 1.95-2.02(m, 1H), 2.24(s, 3H), 2.89-2.96(m, 1H), 3.09-3.15(m, 1H), 3.20-3.31(m, 4H), 3.85-3.91(m, 2H), 4.97(d, 1H, J=4.0Hz), 6.90(bra, 2H), 7.40(d, 1H, J=8.0Hz), 7.62(d, 1H, J=8.0Hz), 7.72(s, 1H)	DMSO-d6, 400MHz
6-20		247 - 248	1.07-1.21(m, 2H), 1.44-1.55(m, 2H), 1.65(s, 6H), 1.70-1.90(m, 5H), 2.16(d, 2H, J=8.0Hz), 2.89-2.98(m, 1H), 7.45(d, 1H, J=8.0Hz), 7.48 and 7.83(bra, 2H), 7.69(dd, 1H, J=8.0, 4.0Hz), 7.80(d, 1H, J=4.0Hz), 12.04(bra, 1H)	DMSO-d6, 400MHz
6-21		>250	1.05-1.19(m, 2H), 1.41-1.55(m, 2H), 1.66(s, 6H), 1.68-1.75(m, 1H), 1.77-1.89(m, 4H), 2.91-3.01(m, 1H), 3.05(d, 2H, J=6.0Hz), 3.56(dd, 2H, J=8.0, 6.0Hz), 4.27(dd, 2H, J=8.0, 6.0Hz), 7.44(d, 1H, J=8.0Hz), 7.71(dd, 1H, J=8.0, 3.0Hz), 7.82(d, 1H, J=3.0Hz)	DMSO-d6, 300MHz
6-22		147(dec.)	1.01-1.14(m, 2H), 1.38-1.53(m, 3H), 1.65(s, 6H), 1.76-1.88(m, 4H), 2.88(t, 1H, J=6.0Hz), 2.88-2.98(m, 2H), 5.34(bra, 2H), 6.00(t, 1H, J=4.5Hz), 7.45(d, 1H, J=8.0Hz), 7.70(dd, 1H, J=8.0, 3.0Hz), 7.81(d, 1H, J=3.0Hz)	DMSO-d6, 300MHz
6-23		160 - 166	0.99-1.13(m, 2H), 1.36-1.51(m, 3H), 1.58(s, 6H), 1.76-1.90(m, 4H), 2.25(s, 3H), 2.86-3.01(m, 1H), 2.88(t, 2H, J=5.8Hz), 5.34(s, 2H), 5.88(t, 1H, J=5.8Hz), 6.89(br, 2H), 7.42(d, 1H, J=8.3Hz), 7.63(dd, 1H, J=1.9, 8.3Hz), 7.73(d, 1H, J=1.9Hz)	DMSO-d6, 300MHz
6-24		213 - 216	0.99-1.16(m, 2H), 1.33-1.62(m, 3H), 1.65(s, 6H), 1.77-1.89(m, 4H), 2.87-2.96(m, 1H), 3.03(t, 2H, J=6.0Hz), 3.81(d, 2H, J=6.0Hz), 5.42(t, 1H, J=6.0Hz), 7.44(d, 1H, J=8.3Hz), 7.52(br, 1H), 7.66-7.73(m, 1H), 7.89(d, 1H, J=8.3Hz), 7.78(br, 1H), 7.81(s, 1H)	DMSO-d6, 300MHz

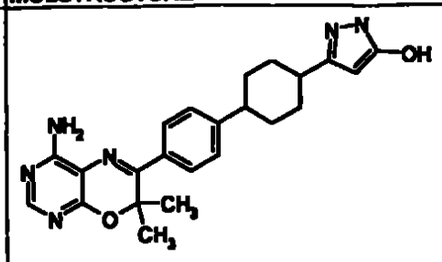
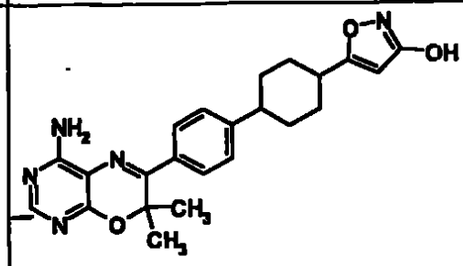
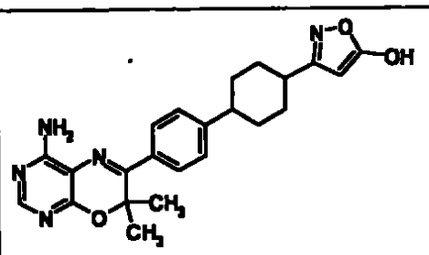
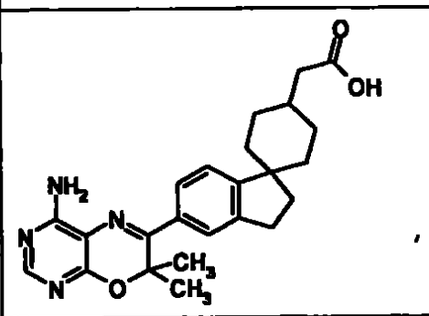
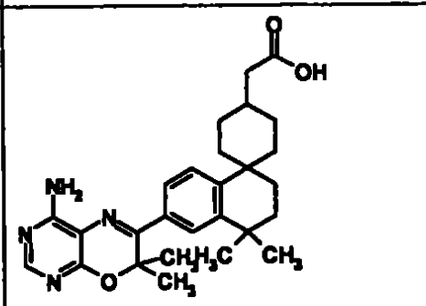
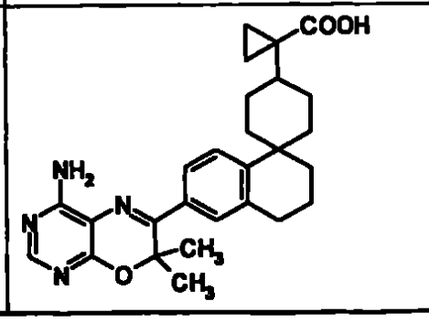
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
6-25		235 - 237	1.16-1.28(m, 2H), 1.43-1.53(m, 2H), 1.65(s, 6H), 1.73-1.87(m, 5H), 2.44(d, 2H, J=8.0Hz), 2.92-2.99(m, 1H), 7.43(d, 1H, J=8.0Hz), 7.69(dd, 1H, J=8.0, 4.0Hz), 7.81(d, 1H, J=4.0Hz)	DMSO-d6, 400MHz

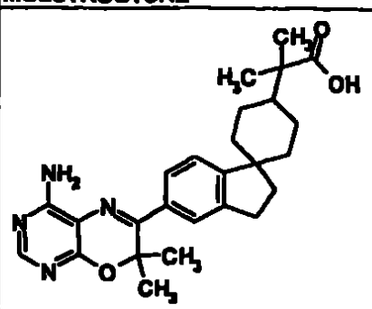
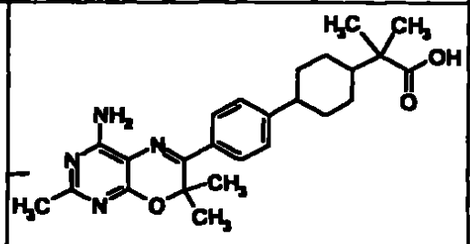
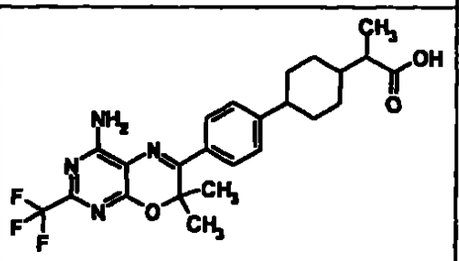
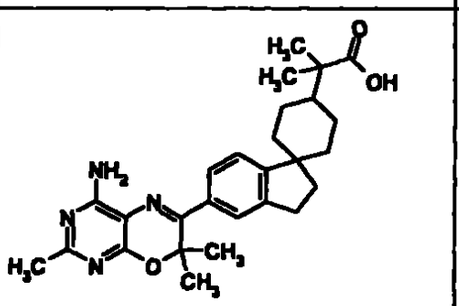
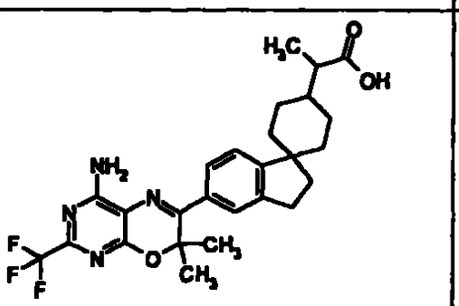
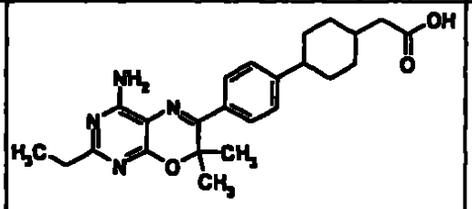
New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
7		>225	1.04-1.19(m, 2H), 1.39-1.55(m, 2H), 1.46(s, 6H), 1.85-1.89(m, 5H), 2.14(d, 2H, J=7.2Hz), 2.21(s, 3H), 2.42-2.52(m, 1H), 6.55(s, 1H), 6.78(br, 2H), 7.23(d, 2H, J=8.3Hz), 7.27(d, 2H, J=8.3Hz), 12.01(s, 1H)	DMSO-d6, 300MHz
7-2			1.05-1.22(m, 2H), 1.13(s, 3H), 1.21(s, 3H), 1.38-1.52(m, 2H), 1.85-1.88(m, 5H), 2.14(d, 2H, J=6.8Hz), 2.20(s, 3H), 2.38-2.70(m, 3H), 2.98-3.04(m, 1H), 6.45(br, 2H), 7.18(d, 2H, J=8.3Hz), 7.22(d, 2H, J=8.3Hz), 11.99(brs, 1H)	DMSO-d6, 300MHz
7-3		>250	1.50(s, 6H), 2.32(s, 3H), 6.58(s, 1H), 6.88(br, 2H), 7.20(d, 2H, J=8.4Hz), 7.28(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
7-4			8.09 (s, 1H), 7.33 (bs, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 6.81 (s, 1H), 2.47 (m, 1H), 2.15 (d, J = 6.9 Hz, 2H), 1.82 (m, 4H), 1.74 (m, 1H), 1.55 (s, 6H), 1.51 (m, 2H), 1.13 (m, 2H)	DMSO-d6, 400MHz
7-5			8.14 (s, 1H), 7.50 (bs, 2H), 7.20 (m, 3H), 6.81 (s, 1H), 2.86 (t, J = 7.2 Hz, 2H), 2.17 (d, J = 6.8 Hz, 2H), 1.96 (t, J = 7.3 Hz, 2H), 1.71 (m, 1H), 1.57 (m, 2H), 1.53 (m, 3H), 1.56 (s, 6H), 1.50 (m, 2H), 1.22 (m, 2H)	DMSO-d6, 400MHz

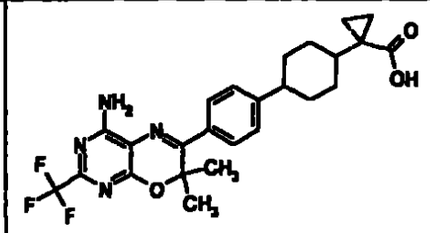
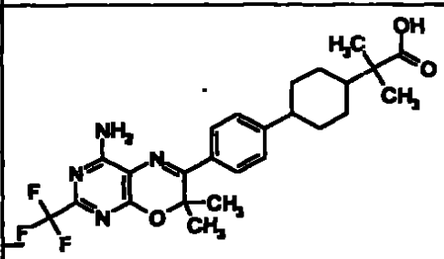
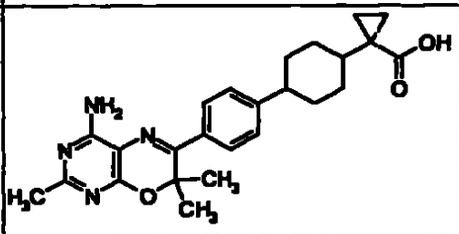
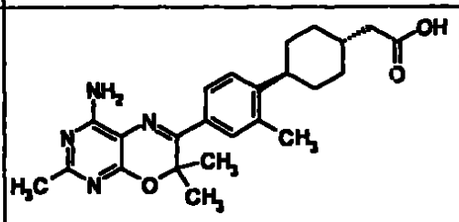
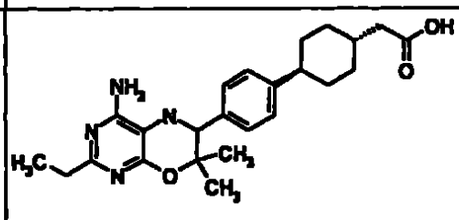
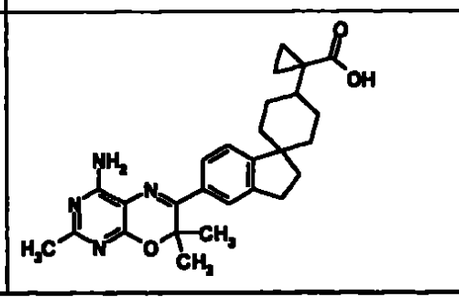
New Ex. No.	MOLSTRUCTURE	m p	NMR(δ)	solvent
9			1.24 (d, J = 6.8 Hz, 3H), 1.25-1.30 (m, 2H), 1.48-1.59 (m, 3H), 1.71 (s, 6H), 1.91-2.00 (m, 4H), 2.38-2.40 (m, 1H), 2.46 (s, 3H), 2.51-2.57 (m, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H)	CDCl3
9-2				
9-3			1.10-1.20 (m, 2H), 1.42-1.90 (m, 13H), 2.17 (d, J = 6.8 Hz, 2H), 2.45-2.60 (m, 1H), 7.34 (d, J = 8 Hz, 2H), 7.36 (brs, 1H), 7.71 (d, J = 8Hz, 2H), 7.74 (brs, 1H), 12.04 (brs, 1H)	DMSO-d6

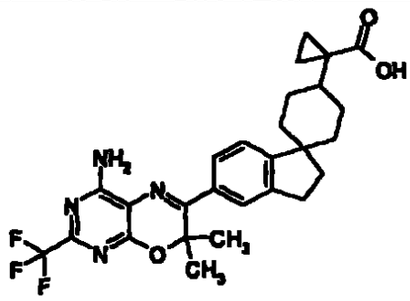
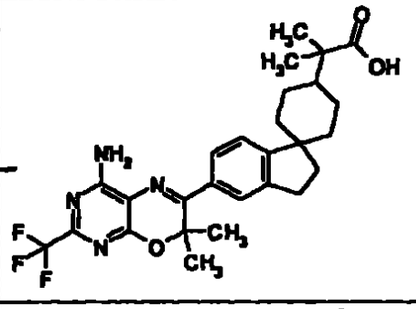
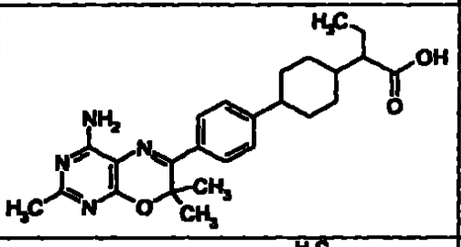
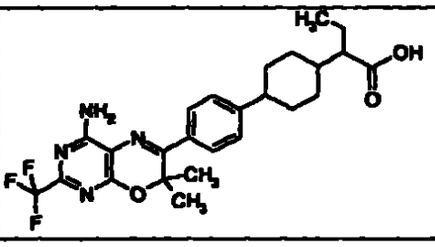
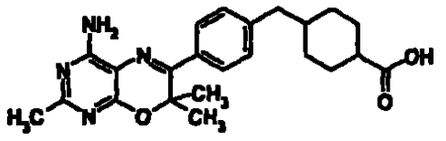
New Ex. No.	MOLSTRUCTURE	mp	NMR(δ)	solvent
10			0.85 (t, J = 7.1 Hz, 3H), 1.05-2.02 (m, 19H), 6.97 (bra, 2H), 7.30 (d, J = 7.8 Hz, 2H), 7.66 (d, J= 7.8 Hz, 2H), 7.95 (s, 1H), 12.05 (s, 1H)	DMSO-d6, 400MHz
10-2			1.78-1.85 (m, 9H), 1.96-2.07 (m, 1H), 2.35-2.48 (m, 4H), 2.86-2.93 (m, 2H), 3.03-4.02 (m, 1H), 3.82 (brd, J = 12 Hz, 1H), 5.81 (s, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.36-7.40 (m, 2H), 8.17 (s, 1H)	CDCl3, 400MHz
10-3			1.06 (s, 6H), 1.14-1.22 (m, 2H), 1.40-1.46 (m, 2H), 1.61-1.75 (m, 10H), 1.82-1.85 (m, 2H), 7.3 (bra, 2H), 7.31 (d, J = 7.7 Hz, 2H), 7.64 (d, J = 7.7 Hz, 2H), 7.99 (s, 1H)	DMSO-d6, 400MHz
10-4			0.87-0.93 (m, 1H), 0.97 (t, J = 4.9 Hz, 1H), 1.02-1.10 (m, 1H), 1.20-1.31 (m, 1H), 1.48 (dd, J = 5.4 Hz, J = 2.1 Hz, 1H), 1.57-1.85 (m, 10H), 1.91-1.98 (m, 1H), 2.63-2.72 (m, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.89 (d, J = 8.3 Hz, 2H), 8.05 (s, 1H)	DMSO-d6, 400MHz
10-5			0.75 (m, 2H), 0.99 (m, 2H), 1.38-1.62 (m, 12H), 1.88-1.87 (m, 4H), 6.97 (br s, 2H), 7.29 (d, J= 8.2Hz, 2H), 7.83 (d, J = 8.2Hz, 2H), 7.94 (s, 1H), 12.00 (s, 1H)	DMSO-d6, 400MHz
10-6			1.25-1.55 (m, 4H), 1.59 (s, 6H), 1.62-1.72 (m, 3H), 1.80-1.87 (m, 2H), 2.43-2.55 (m, 1H), 3.82 (br s, 1H), 5.05 (bra, 1H), 6.98 (bra, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.84 (d, J = 8.2 Hz, 2H), 7.94 (s, 1H), 12.03 (bra, 1H)	DMSO-d6, 400MHz

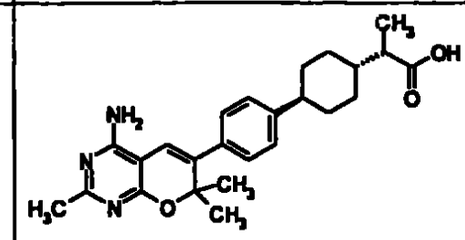
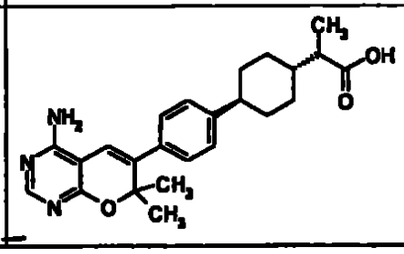
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New Ex. No.	MOLSTRUCTURE	m p	NMR(δ)	solvent
10-7			1.5-1.85 (m, 6H), 1.80 (s, 6H), 2.06 (m, 2H), 2.22 (m, 2H), 2.72-2.90 (m, 2H), 5.67 (s, 1H), 7.20-7.5 (m, 2H), 7.51 (d, J= 6.2 Hz, 2H), 7.84 (d, J= 6.2 Hz, 2H), 8.18 (s, 1H)	DMSO-d6, 400MHz
10-8			1.5-1.85 (m, 6H), 1.78 (s, 6H), 2.0-2.1 (m, 2H), 2.2-2.3 (m, 2H), 2.75-2.95 (m, 2H), 5.94 (s, 1H), 7.10-7.2 (m, 1H), 7.50 (d, J= 5.5 Hz, 2H), 7.83 (d, J= 5.5 Hz, 2H), 8.12 (s, 1H)	DMSO-d6, 400MHz
10-9			1.50-1.85 (m, 6H), 1.77 (s, 6H), 2.0-2.1 (m, 2H), 2.2-2.3 (m, 2H), 2.85-2.85 (m, 2H), 5.30 (s, 1H), 7.10-7.20 (m, 1H), 7.49 (d, J= 6.1 Hz, 2H), 7.81 (d, J= 6.1 Hz, 2H), 8.11 (s, 1H)	DMSO-d6, 400MHz
10-10			1.05-1.20 (m, 2H), 1.35-2.07 (m, 15H), 2.15 (d, J = 6.9Hz, 2H, major isomer only), 2.28 (d, J = 7.4 Hz, 2H, minor isomer only), 2.77-2.80 (m, 2H), 5.97 (br s, 2H), 7.03 (d, J = 7.9 Hz, 1H), 7.25-7.30 (m, 2H), 7.97 (s, 1H)	CDCl3, 400MHz
10-11			1.05-1.17 (m, 8H), 1.35-1.71 (m, 17H), 2.02 (d, J = 6.9 Hz, 2H), 6.37 (brs, 2H), 7.13-7.21 (m, 2H), 7.31 (s, 1H), 7.88 (s, 1H)	CDCl3, 400MHz
10-12			0.72-0.76 (m, 2H), 0.99 -1.03 (m, 2H), 1.40-1.82 (m, 19H), 2.75 (t, J = 6.0 Hz), 7.15 (brs, 2H), 7.36 (s, 1H), 7.46 (s, 2H), 7.99 (s, 1H)	DMSO-d6, 400MHz

New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
10-13			1.23 (s, 6H), 1.21-1.45 (m, 4H), 1.55-1.85 (m, 7H), 1.81 (s, 6H), 2.06 (m, 2H), 2.96 (m, 2H), 7.25 (m, 1H), 7.51-7.54 (m, 3H), 12.0 (brs, 1H)	DMSO-d6, 400MHz
10-14			1.06 (s, 6H), 1.15-1.26 (m, 2H), 1.42-1.51 (m, 2H), 1.60-1.66 (m, 7H), 1.68-1.73 (m, 2H), 1.82-1.89 (m, 2H), 2.34 (s, 3H), 2.50-2.53 (m, 1H), 7.31 (d, J = 6.0 Hz, 2H), 7.55 (brs, 2H), 7.66 (d, J = 6.0 Hz, 2H)	DMSO-d6, 400MHz
10-15			1.06 (d, J = 5.6 Hz, 3H), 1.13-1.24 (m, 2H), 1.42-1.53 (m, 2H), 1.54-1.60 (m, 7H), 1.71-1.92 (m, 4H), 2.19 (quin, J = 5.6 Hz, 1H), 2.51-2.58 (m, 1H), 7.32 (d, J = 6.8 Hz, 2H), 7.69 (d, J = 6.8 Hz, 2H), 12.06 (brs, 1H)	DMSO-d6, 400MHz
10-16			1.23 (s, 6H), 1.20-1.50 (m, 3H), 1.55-1.85 (m, 7H), 1.80 (s, 6H), 2.06 (m, 2H), 2.65 (s, 3H), 2.96 (m, 2H), 6.50 (bs, 1H), 7.25 (m, 1H), 7.51-7.54 (m, 2H), 10.75 (brs, 1H)	CDCl3, 400MHz
10-17			1.24 (d, J = 7.0 Hz, 3H), 1.20-1.50 (m, 3H), 1.55-1.85 (m, 7H), 1.75 (s, 6H), 2.05 (m, 2H), 2.48 (m, 1H), 2.96 (m, 2H), 5.76 (brs, 1H), 7.15-7.25 (m, 3H), 7.46-7.50 (m, 1H)	CDCl3, 400MHz
10-18			1.12-1.22 (m, 5H), 1.46-1.54 (m, 2H), 1.60 (s, 6H), 1.75-1.88 (m, 5H), 2.16 (d, J = 7.2 Hz, 2H), 2.45-2.53 (m, 1H), 3.42-3.48 (m, 2H), 7.40 (brs, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 12.05 (brs, 1H)	DMSO-d6, 400MHz

New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
10-19			0.84-0.89 (m, 2H), 1.27-1.33 (m, 2H), 1.44-1.53 (m, 5H), 1.76 (s, 6H), 1.84-1.90 (m, 2H), 1.94-2.01 (m, 2H), 2.55-2.62 (m, 1H), 5.75 (brs, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H)	CDCl3, 400MHz
10-20			1.23 (s, 6H), 1.25-1.55 (m, 5H), 1.76 (s, 6H), 1.83-1.89 (m, 2H), 1.98-2.04 (m, 2H), 2.52-2.60 (m, 1H), 5.70 (brs, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H)	CDCl3, 400MHz
10-21			0.83-0.88 (m, 2H), 1.27-1.31 (m, 2H), 1.47-1.60 (m, 5H), 1.72 (s, 6H), 1.85-1.91 (m, 2H), 1.93-2.00 (m, 2H), 2.44 (s, 3H), 2.55-2.62 (m, 1H), 6.13 (brs, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H)	CDCl3, 400MHz
10-22			1.11-1.22 (m, 2H), 1.43-1.51 (m, 13H), 2.16 (d, J = 5.3 Hz, 2H), 2.34 (s, 3H), 2.35 -(s, 3H), 2.62-2.74 (m, 1H), 7.29 (d, J = 6.5 Hz, 1H), 7.46-7.52 (m, 4H)	DMSO-d6, 400MHz
10-23			1.08-1.21 (m, 11H), 1.42-1.53 (m, 2H), 1.69-87 (m, 5H), 2.15 (d, J = 7.2 Hz, 2H), 2.42-2.52 (m, 3H), 4.07 (s, 1H), 5.10 (s, 1H), 6.14 (s, 2H), 7.26 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 12.05 (brs, 1H)	DMSO-d6, 400MHz
10-24			0.88 (m, 2H), 1.3 (m, 2H), 1.50-1.99 (m, 10H), 1.79 (s, 6H), 2.1 (m, 2H), 2.65 (s, 3H), 2.96 (m, 2H), 6.5 (brs, 1H), 7.15-7.25 (m, 1H), 7.45-7.50 (m, 2H), 10.5 (brs, 1H)	CDCl3, 400MHz

New Ex. No.	MOLSTRUCTURE	m.p.	NMR(δ)	solvent
10-25			0.76 (m, 2H), 1.02 (m, 2H), 1.45-1.83 (m, 10H),1.7 (s, 6H), 2.0 (m, 2H), 2.95 (m, 2H), 3.33 (m, 1H), 7.15-7.25 (m, 1H), 7.45-7.50 (m, 2H), 12.0 (brs, 1H)	CDCl3, 400MHz
10-26			1.0 (m, 2H), 1.23 (s, 6H), 1.20-1.50 (m, 3H), 1.55-1.85 (m, 6H), 1.76 (s, 6H), 2.08 (m, 2H), 2.95 (m, 2H), 5.91 (brs, 1H), 7.15-7.25 (m, 2H), 7.45-7.50 (m, 1H)	CDCl3, 400MHz
10-27			0.86 (t, J = 7.2 Hz, 3H), 1.05-1.12 (m, 2H), 1.33-1.80 (m, 10H), 1.70-2.04 (m, 6H), 2.25 (s, 3H), 2.45-2.52 (m, 1H), 6.80 (brs, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H)	DMSO-d6, 400MHz
10-28			0.99 (t, J = 7.2 Hz, 3H), 1.25-1.25 (m, 18H), 2.50-2.60 (m, 1H), 5.76 (brs, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H)	CDCl3, 400MHz
10-29			0.90-1.05 (m,1H), 1.10-1.28 (m, 2H), 1.40-1.50 (m, 2H), 1.57 (s, 6H), 1.60-1.70 (m, 2H), 1.80-1.90 (m, 2H), 1.90 (s, 2H), 2.24 (s, 3H), 2.35-2.50 (m, 1H), 6.81 (brs, 2H), 7.21 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.2 Hz, 2H), 11.9 (brs, 1H)	DMSO-d6, 400MHz

New Ex. No.	MOLSTRUCTURE	m p	NMR(δ)	solvent
10-30			1.05 (d, J = 6.9 Hz, 3H), 1.10-1.28 (m, 2H), 1.41-1.51 (m, 2H), 1.52-2.01 (m, 7H), 1.71-1.87 (m, 4H), 2.15-2.22 (m, 1H), 2.39 (s, 3H), 2.44-2.50 (m, 1H), 6.65 (s, 1H), 7.30 (Abq, J = 8.0 Hz 2H), 8.0 (bra, 2H)	DMSO-d6, 400MHz
10-31			1.05 (d, J = 6.9 Hz, 3H), 1.10-1.25 (m, 2H), 1.41-1.62 (m, 9H), 1.71-1.88 (m, 4H), 2.14-2.21 (m, 1H), 2.42-2.50 (m, 1H), 6.58 (s, 1H), 7.03 (bra, 2H), 7.27 (Abq, J = 7.9 Hz 2H), 12.0 (bra, 1H)	DMSO-d6, 400MHz

Example 10

[0246] This example describes assays that may be used to identify compounds having DGAT activity.

[0247] Numerous *in vitro* assay systems may be used to determine the modulation of DGAT activity. Examples of such assay systems utilize insect cell over-expression systems, tissue microsome preparations and cell culture. In the insect cell over-expression and tissue microsome preparation assay systems, the system itself provides the enzyme source for activity measurements. Such measurements are generally conducted using radiolabeled substrate, wherein the radiolabeled product that is generated is subsequently resolved by thin layer chromatography (TLC) (*see, e.g.*, Cases, *et al., Proc. Natl. Acad. Sci.* (1998) 95:13018 and Cases, *et al., J. Biol. Chem.* (2001) 276:38870).

[0248] By comparison, cell culture-based assay systems measure intracellular synthesis of triglyceride by incubating living cells with radiolabeled fatty acid. The radiolabeled fatty acid is utilized in triglyceride biosynthesis. Triglycerides can then be extracted from the cells using organic solvent and resolved by thin layer chromatography to determine the level of radiolabel incorporation as a measure of enzyme activity (*see e.g.*, Cases, *et al., J. Biol. Chem.* (2001) 276:38870).

Cell-Based Assays

[0249] In a preferred cellular assay, human colon tumor CaCO2, human hepatoma HepG2, or mouse adipocyte 3T3-L1 cells (undifferentiated or differentiated as described below) are cultured to confluency in 24 well plates. The medium is replaced with serum-free medium and the cells incubated for a further 24-48 h. Next, medium is replaced with serum-free medium containing 400 μM oleic acid (complexed with BSA, 2:1 mole:mole) and compound at varying doses in a final volume of 200 μL per well. Cells are incubated for 30 min. before adding 0.1 μCi of ^{14}C oleic acid directly to the cells and the incubation continued for 10-30 min. depending on the cell type. Cells are washed two times with 1 mL PBS and air dried at 37°C for 10 min. Cell lipids are extracted with 0.5 mL hexane:isopropyl alcohol (3:2 v/v) for 5 min. twice. Lipid extracts are evaporated to dryness and used for TLC using hexane:ethyl ether:acetic acid (80:20:1 v/v) as solvent. The radioactive bands are visualized and quantified by exposure to X-ray film or phosphorimager screen.

[0250] 3T3-L1 cell differentiation into adipocytes is induced by incubating confluent cells in medium containing 10% serum, insulin (10 μg/mL), dexamethasone (1 μM), isobutylmethyl xanthine (IBMX, 0.5 mM), and tri-iodothyronine (T3, 10 nM). After 2 days, cells are maintained in serum, insulin, T3, and BRL49653 (1 μM) containing medium for 4-10 days.

Biochemical Assays

[0251] A preferred assay that may be used for identifying DGAT inhibitors involves a high throughput screening Scintillation Proximity Assay (SPA). In such an assay human DGAT1 is cloned from a human liver cDNA library. PCR is used to add a restriction site and flag epitope at the most 5' end and a restriction site at the 3' end of the sequence. Thereafter, human flagtag (FT) DGAT1 baculovirus may be generated using a Bac-to-Bac Baculovirus Expression System® (Invitrogen). Insect cells (*e.g.*, sf9, sf21, or High Five) are infected for 24 to 72 h and collected by centrifugation. Cell pellets are resuspended in homogenization buffer and lysed using a homogenization device, such as a Microfluidizer. Total cell membranes are collected by ultracentrifugation at 45,000 rpm for 1 h.

[0252] A small aliquot (0.2 μg/well) of membrane is incubated with 10μM compound or mercuric chloride (as positive control for inhibition) in the presence of enzyme substrate, dioleoyl glycerol (200μM) in 384 well plates, final volume 50 μL per well. The reaction is started by the addition of radioactive substrate, ^{14}C acyl coenzyme A (25μM, such as decanoyl CoA, palmitoyl CoA, oleoyl CoA), and incubated at room temperature for 2 h. The reaction is stopped by adding Wheat Germ Agglutinin (WGA) SPA beads (0.2 mg) in mercuric chloride. Cell membranes are allowed to couple to the beads overnight. The signal can be measured using, for example, a Chemiluminescence Image Plate Reader (CLIPR) or TopCount device.

[0253] Compounds of the present invention assessed by the above-described assay were found to have DGAT-inhibiting activity. *See* Table 11 below.

Table 11

Example	hDGAT1 IC_{50}*	Example	hDGAT1 IC_{50}*	Example	hDGAT1 IC_{50}*
1	+	2-6	++	2-48	++
1-2	+	2-7	++	2-49	++
1-3	+	2-8	+	2-50	++
1-4	+	2-9	+	2-51	++
1-5	+	2-10	+	2-52	++
1-6	+	2-11	+	2-53	++
1-7	+	2-12	+	2-54	++
1-8	+	2-13	+	2-55	++
1-9	+	2-14	+	2-58	++
1-10	+	2-15	+	2-59	++
1-11	+	2-16	+	2-60	++
1-12	+	2-17	+	2-61	++
1-13	+	2-18	++	2-62	++
1-14	+	2-19	+	2-63	++
1-15	+	2-20	+	2-64	++
1-16	+	2-21	+	2-65	+++
1-17	+	2-22	+	2-66	+
1-18	+	2-23	+	2-67	++
1-19	+	2-24	+	2-68	+
1-20	+	2-25	+	2-69	+++
1-21	+	2-26	++	2-70	++
1-22	+	2-27	+	2-71	+
1-23	+	2-28	+	2-72	++
1-24	+	2-29	+	2-73	++
1-25	+	2-30	+	2-74	+++
1-26	+	2-31	+	2-75	+
1-27	+	2-32	+	2-76	++
1-28	+	2-33	++	2-77	++
1-29	+	2-34	++	2-78	++
1-30	+	2-35	+	2-79	++
1-31	+	2-36	++	2-80	++
1-32	+	2-37	+	2-81	+
1-33	+	2-38	+	2-82	+
1-34	+	2-39	+	2-83	+
1-35	+	2-40	+++	2-84	+
1-36	+	2-41	+	2-85	+
1-37	+	2-42	++	2-86	+
2	+++	2-43	++	2-87	+
2-2	++	2-44	++	2-88	+
2-3	++	2-45	++	2-89	+
2-4	+++	2-46	++	2-90	+
2-5	++	2-47	++	2-91	++

Example	hDGAT1 IC_{50}*
2-92	++
2-93	++
2-94	++
2-95	++
2-96	++
2-97	++
2-98	++
2-99	++
2-100	++
2-101	++
2-102	++
2-103	++
2-104	++
2-105	++
2-106	++
2-107	+++
2-108	++
2-109	++
2-110	++
2-111	++
2-112	++
2-113	++
2-114	++
2-115	+
2-116	++
2-117	++
2-118	++
2-119	++
2-120	++
2-121	++
2-122	++
2-123	++
2-124	++
2-125	+++
2-126	++
2-127	++
2-128	++
2-129	++
2-130	++
2-131	++
2-132	++
2-133	++
2-134	+++
2-135	++
2-136	++
2-137	+++
2-138	++
2-139	++
2-140	++
2-141	++
2-142	++
2-143	+++
2-144	++
2-145	++
2-146	++
2-147	++
2-148	+++
2-149	++
2-150	++
2-151	+++
2-152	++
2-153	+++
2-154	++
2-155	++
2-156	++
2-157	+++
2-158	++
2-159	++
2-160	++
2-161	++
2-162	++
2-163	++
2-164	++
2-165	++
2-166	++
2-167	++
2-168	++
2-169	++
2-170	++
2-171	+
2-172	++
2-173	++
2-174	++
2-175	++
2-176	++
2-177	++
2-178	++
2-179	++
2-180	++
2-181	++
2-182	++
2-183	++
2-184	++
2-185	++
2-186	++
2-187	+++
2-188	++
2-189	++
2-190	++
2-191	+++
2-192	+++
2-193	++
2-194	++
2-195	++
2-196	++
2-197	++
2-198	++
2-200	+++
2-201	+++
2-202	++
2-203	++
2-204	++
2-205	++
2-206	++
2-207	++
2-208	++
2-209	++
2-210	++
2-211	++
2-212	+++
2-213	++
2-214	+++
2-215	++
2-216	++
2-217	++
2-218	++
2-219	++
2-220	++
2-221	+
2-222	+
2-223	+
2-224	+
2-225	+
2-226	+
2-227	+
2-228	+
2-229	+
2-230	++

Example	hDGAT1 IC_{50}*
2–232	++
2–233	+
2–234	++
2–235	++
2–236	++
2–237	++
2–238	+
2–239	+
2–240	++
2–241	++
2–242	+
2–243	++
2–244	++
2–245	++
2–246	++
2–247	++
2–248	++
2–249	++
2–250	++
2–251	++
2–252	++
2–253	+++
2–254	++
2–255	++
2–256	++
2–257	++
2–258	++
2–259	++
2–260	++
2–261	++
2–262	++
2–263	+++
2–264	++
3	++
3–2	+
3–3	+
4	+
4–2	+
4–3	+

Example	hDGAT1 IC_{50}*
4–4	++
4–5	+
4–6	+
4–7	+
5	+
5–2	+
5–3	+
6	+++
6–2	++
6–3	++
6–4	+
6–8	++
6–9	+++
6–10	++
6–11	++
6–12	+++
6–13	+++
6–14	++
6–15	++
6–16	+
6–17	+
6–18	++
6–19	++
6–20	+++
6–21	++
6–22	++
6–23	++
6–24	++
6–25	++
7	++
7–2	++
7–3	+
7–4	++
7–5	++
8	+++
8–2	++
8–3	++
8–4	++
8–5	++

Example	hDGAT1 IC_{50}*
8–6	++
8–7	+++
9	++
9–2	++
9–3	+++
10	+++
10–2	++
10–3	+++
10–4	++
10–5	++
10–6	++
10–7	++
10–8	++
10–9	++
10–10	+++
10–11	++
10–12	++
10–13	+++
10–14	++
10–15	+++
10–16	++
10–17	+++
10–18	++
10–19	++
10–20	++
10–21	++
10–22	++
10–23	++
10–24	++
10–25	++
10–26	++
10–27	++
10–28	+++
10–29	++
10–30	++
10–31	++

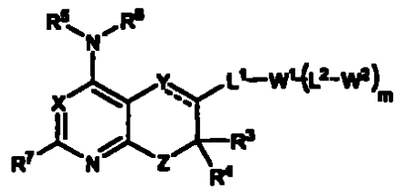
** Legend:* *"+" represents: IC_{50} value > 0.1μM*
"++" represents: 0.1μM ≥IC_{50} value ≥0.01μM
"+++" represents: IC_{50} value < 0.01μM

[0254] All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the

foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

WHAT IS CLAIMED IS:

1. A compound of formula (I):



I

or a pharmaceutically acceptable salt, prodrug or stereoisomer thereof, wherein

X is selected from the group consisting of $C(R^1)$ and N;

Y is selected from the group consisting of $C(R^1)$, $C(R^2)(R^2)$, N and $N(R^2)$;

Z is selected from the group consisting of O and S;

W^1 is a substituted or unsubstituted member selected from the group consisting of cyclo(C_3-C_8)alkyl, heterocyclo(C_3-C_8)alkyl, aryl and heteroaryl;

W^2 is a substituted or unsubstituted member selected from the group consisting of cyclo(C_3-C_8)alkyl, heterocyclo(C_3-C_8)alkyl, aryl and heteroaryl;

L^1 is selected from the group consisting of a bond, (C_1-C_4)alkylene, (C_2-C_4)alkenylene, O and $N(R^a)C(O)$;

L^2 is selected from the group consisting of a bond, O, (C_1-C_4)alkylene, (C_2-C_4)alkenylene, (C_1-C_4)heteroalkylene and $N(R^a)C(O)$;

the subscript m is 0 or 1;

optionally, when m is 1 and L^2 is a bond, a substituent on W^2 may be combined with a substituent on W^1 to form a 5-, 6- or 7-membered ring fused to W^1 and spiro or fused to W^2, wherein said ring is saturated or unsaturated and has 0, 1 or 2 heteroatoms selected from the group consisting of N, O and S as ring members;

each R^1 is independently selected from the group consisting of H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, fluoro(C_1-C_8)alkyl, aryl, aryl(C_1-C_4)alkyl, $C(O)R^a$, CO_2R^a and $C(O)NR^aR^b$;

each R^2 is independently selected from the group consisting of H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, fluoro(C_1-C_8)alkyl, $C(O)R^a$, CO_2R^a, $C(O)NR^aR^b$, aryl and aryl(C_1-C_4)alkyl;

R^3 and R^4 are independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $C(O)R^a$, CO_2R^a, $C(O)NR^aR^b$ and $(C_1$-$C_4)$alkylene-OR^a;

optionally, R^3 and R^4 may be combined to form a 3-, 4-, 5- or 6-membered spiro ring;

optionally, R^2, R^3 or R^4 may be combined with W^1 to form a 5-, 6- or 7-membered fused ring having from 0 to 3 heteroatoms selected from the group consisting of N, O and S;

R^5 and R^6 are independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $C(O)R^a$ and CO_2R^a;

optionally, R^5 and R^6 may be combined with the nitrogen atom to form a 5-, 6- or 7-membered ring;

optionally, when X is $C(R^1)$ or when Y includes an R^1 or R^2 group, R^5 or R^6 may be combined with R^1 or R^2 to form a 5-, 6- or 7-membered fused ring containing the nitrogen atom to which R^5 or R^6 is attached;

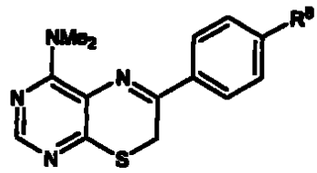
R^7 is selected from the group consisting of H, $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_4)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $C(O)R^a$, OR^a and NR^aR^b;

optionally, when X is $C(R^1)$, R^7 may be combined with R^1 to form a 5-, 6- or 7-membered fused ring;

each R^a and R^b is independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, fluoro$(C_1$-$C_8)$alkyl, aryl and aryl$(C_1$-$C_4)$alkyl; and

the dotted line indicates an optional bond;

with the proviso that said compound is other than



wherein R^8 is selected from the group consisting of H, NO_2, Cl, methoxy, methyl and phenyl.

2. A compound of claim 1, wherein X is N.

3. A compound of claim 2, wherein Z is O.

4. A compound of claim 3, wherein L^1 is a bond and W^1 is a substituted or unsubstituted member selected from the group consisting of benzene, pyridine, thiophene, oxazole, thiazole, benzoxazole, benzthiazole, benzofuran, benzothiophene, (C_4-C_7)cycloalkane, (C_5-C_7)cycloalkene, 1,2,3,4-tetrahydronaphthalene and indane.

5. A compound of claim 4, wherein W^1 is a substituted or unsubstituted member selected from the group consisting of benzene, pyridine , thiophene, 1,2,3,4-tetrahydronaphthalene and indane.

6. A compound of claim 5, wherein the subscript m is 1.

7. A compound of claim 5, wherein the subscript m is 1 and L^2 is a bond.

8. A compound of claim 7, wherein W^2 is a substituted or unsubstituted member selected from the group consisting of benzene, pyridine, (C_4-C_7)cycloalkane, (C_5-C_7)cycloalkene, pyrrolidine, piperidine, piperazine and morpholine.

9. A compound of claim 4, wherein R^5 and R^6 are independently selected from the group consisting of H, (C_1-C_8)alkyl, $C(O)R^a$ and CO_2R^a.

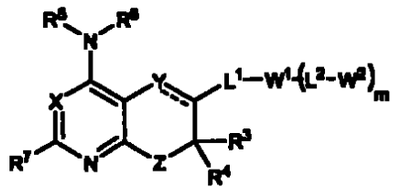
10. A compound of claim 9, wherein R^5 and R^6 are independently selected from the group consisting of H and (C_1-C_8)alkyl.

11. A compound of claim 10, wherein R^3 and R^4 are independently selected from the group consisting of H and (C_1-C_8)alkyl.

12. A compound of claim 11, wherein R^7 is selected from the group consisting of H, (C_1-C_8)alkyl, halo(C_1-C_4)alkyl, OH and NR^aR^b wherein R^a and R^b are independently selected from the group consisting of H and (C_1-C_8)alkyl.

13. A compound of claim 11, wherein R^7 is H, (C_1-C_8)alkyl or halo(C_1-C_4)alkyl.

14. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of formula (I):



I

or a pharmaceutically acceptable salt, prodrug or stereoisomer thereof, wherein

X is selected from the group consisting of $C(R^1)$ and N;

Y is selected from the group consisting of $C(R^1)$, $C(R^2)(R^2)$, N and $N(R^2)$;

Z is selected from the group consisting of O and S;

W^1 is a substituted or unsubstituted member selected from the group consisting of cyclo$(C_3$-$C_8)$alkyl, heterocyclo$(C_3$-$C_8)$alkyl, aryl and heteroaryl;

W^2 is a substituted or unsubstituted member selected from the group consisting of cyclo$(C_3$-$C_8)$alkyl, heterocyclo$(C_3$-$C_8)$alkyl, aryl and heteroaryl;

L^1 is selected from the group consisting of a bond, $(C_1$-$C_4)$alkylene, $(C_2$-$C_4)$alkenylene, O and $N(R^a)C(O)$;

L^2 is selected from the group consisting of a bond, O, $(C_1$-$C_4)$alkylene, $(C_2$-$C_4)$alkenylene, $(C_1$-$C_4)$heteroalkylene and $N(R^a)C(O)$;

the subscript m is 0 or 1;

optionally, when m is 1 and L^2 is a bond, a substituent on W^2 may be combined with a substituent on W^1 to form a 5-, 6- or 7-membered ring fused to W^1 and spiro or fused to W^2, wherein said ring is saturated or unsaturated and has 0, 1 or 2 heteroatoms selected from the group consisting of N, O and S as ring members;

each R^1 is independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, fluoro$(C_1$-$C_8)$alkyl, aryl, aryl$(C_1$-$C_4)$alkyl, $C(O)R^a$, CO_2R^a and $C(O)NR^aR^b$;

each R^2 is independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, fluoro$(C_1$-$C_8)$alkyl, $C(O)R^a$, CO_2R^a, $C(O)NR^aR^b$, aryl and aryl$(C_1$-$C_4)$alkyl;

R^3 and R^4 are independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $C(O)R^a$, CO_2R^a, $C(O)NR^aR^b$ and $(C_1$-$C_4)$alkylene-OR^a;

optionally, R^3 and R^4 may be combined to form a 3-, 4-, 5- or 6-membered spiro ring;

optionally, R^2, R^3 or R^4 may be combined with W^1 to form a 5-, 6- or 7-membered fused ring having from 0 to 3 heteroatoms selected from the group consisting of N, O and S;

R^5 and R^6 are independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $C(O)R^a$ and CO_2R^a;

optionally, R^5 and R^6 may be combined with the nitrogen atom to form a 5-, 6- or 7-membered ring;

optionally, when X is $C(R^1)$ or when Y includes an R^1 or R^2 group, R^5 or R^6 may be combined with R^1 or R^2 to form a 5-, 6- or 7-membered fused ring containing the nitrogen atom to which R^5 or R^6 is attached;

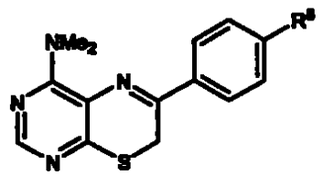
R^7 is selected from the group consisting of H, $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_4)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $C(O)R^a$, OR^a and NR^aR^b;

optionally, when X is $C(R^1)$, R^7 may be combined with R^1 to form a 5-, 6- or 7-membered fused ring;

each R^a and R^b is independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, fluoro$(C_1$-$C_8)$alkyl, aryl and aryl$(C_1$-$C_4)$alkyl; and

the dotted line indicates an optional bond;

with the proviso that said compound is other than



wherein R^8 is selected from the group consisting of H, NO_2, Cl, methoxy, methyl and phenyl.

15. A pharmaceutical composition of claim 14, wherein X is N.

16. A pharmaceutical composition of claim 15, wherein Z is O.

17. A pharmaceutical composition of claim 16, wherein L^1 is a bond and W^1 is a substituted or unsubstituted member selected from the group consisting of benzene, pyridine, thiophene, oxazole, thiazole, benzoxazole, benzthiazole, benzofuran, benzothiophene, $(C_4$-$C_7)$cycloalkane, $(C_5$-$C_7)$cycloalkene, 1,2,3,4-tetrahydronaphthalene and indane.

18. A pharmaceutical composition of claim 17, wherein W^1 is a substituted or unsubstituted member selected from the group consisting of benzene, pyridine, thiophene, 1,2,3,4-tetrahydronaphthalene and indane.

19. A pharmaceutical composition of claim 18, wherein the subscript m is 1.

20. A pharmaceutical composition of claim 18, wherein the subscript m is 1 and L^2 is a bond.

21. A pharmaceutical composition of claim 20, wherein W^2 is a substituted or unsubstituted member selected from the group consisting of benzene, pyridine, $(C_4$-$C_7)$cycloalkane, $(C_5$-$C_7)$cycloalkene, pyrrolidine, piperidine, piperazine and morpholine.

22. A pharmaceutical composition of claim 17, wherein R^5 and R^6 are independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $C(O)R^a$ and CO_2R^a.

23. A pharmaceutical composition of claim 22, wherein R^5 and R^6 are independently selected from the group consisting of H and $(C_1$-$C_8)$alkyl.

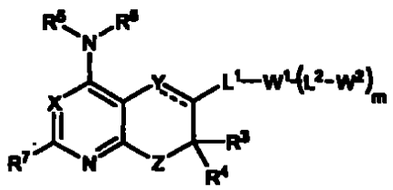
24. A pharmaceutical composition of claim 23, wherein R^3 and R^4 are independently selected from the group consisting of H and $(C_1$-$C_8)$alkyl.

25. A pharmaceutical composition of claim 24, wherein R^7 is selected from the group consisting of H, $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_4)$alkyl, OH and NR^aR^b wherein R^a and R^b are independently selected from the group consisting of H and $(C_1$-$C_8)$alkyl.

26. A pharmaceutical composition of claim 24, wherein R^7 is H, $(C_1$-$C_8)$alkyl or halo$(C_1$-$C_4)$alkyl.

27. A method of treating a disease or condition selected from the group consisting of obesity, diabetes, anorexia nervosa, bulimia, cachexia, syndrome X, insulin resistance, hyperglycemia, hyperuricemia, hyperinsulinemia, hypercholesterolemia, hyperlipidemia, dyslipidemia, mixed dyslipidemia, hypertriglyceridemia, nonalcoholic fatty liver disease, atherosclerosis, arteriosclerosis, acute heart failure, congestive heart failure, coronary artery disease, cardiomyopathy, myocardial infarction, angina pectoris, hypertension, hypotension, stroke, ischemia, ischemic reperfusion injury, aneurysm,

restenosis, vascular stenosis, solid tumors, skin cancer, melanoma, lymphoma, breast cancer, lung cancer, colorectal cancer, stomach cancer, esophageal cancer, pancreatic cancer, prostate cancer, kidney cancer, liver cancer, bladder cancer, cervical cancer, uterine cancer, testicular cancer and ovarian cancer, comprising administering to a subject in need thereof an effective amount of a compound of formula (I):



I

or a pharmaceutically acceptable salt, prodrug or stereoisomer thereof, wherein

X is selected from the group consisting of $C(R^1)$ and N;

Y is selected from the group consisting of $C(R^1)$, $C(R^2)(R^2)$, N and $N(R^2)$;

Z is selected from the group consisting of O and S;

W^1 is a substituted or unsubstituted member selected from the group consisting of cyclo$(C_3$-$C_8)$alkyl, heterocyclo$(C_3$-$C_8)$alkyl, aryl and heteroaryl;

W^2 is a substituted or unsubstituted member selected from the group consisting of cyclo$(C_3$-$C_8)$alkyl, heterocyclo$(C_3$-$C_8)$alkyl, aryl and heteroaryl;

L^1 is selected from the group consisting of a bond, $(C_1$-$C_4)$alkylene, $(C_2$-$C_4)$alkenylene, O and $N(R^a)C(O)$;

L^2 is selected from the group consisting of a bond, O, $(C_1$-$C_4)$alkylene, $(C_2$-$C_4)$alkenylene, $(C_1$-$C_4)$heteroalkylene and $N(R^a)C(O)$;

the subscript m is 0 or 1;

optionally, when m is 1 and L^2 is a bond, a substituent on W^2 may be combined with a substituent on W^1 to form a 5-, 6- or 7-membered ring fused to W^1 and spiro or fused to W^2, wherein said ring is saturated or unsaturated and has 0, 1 or 2 heteroatoms selected from the group consisting of N, O and S as ring members;

each R^1 is independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, fluoro$(C_1$-$C_8)$alkyl, aryl, aryl$(C_1$-$C_4)$alkyl, $C(O)R^a$, CO_2R^a and $C(O)NR^aR^b$;

each R^2 is independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, fluoro$(C_1$-$C_8)$alkyl, $C(O)R^a$, CO_2R^a, $C(O)NR^aR^b$, aryl and aryl$(C_1$-$C_4)$alkyl;

R^3 and R^4 are independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $C(O)R^a$, CO_2R^a, $C(O)NR^aR^b$ and $(C_1$-$C_4)$alkylene-OR^a;

optionally, R^3 and R^4 may be combined to form a 3-, 4-, 5- or 6-membered spiro ring;

optionally, R^2, R^3 or R^4 may be combined with W^1 to form a 5-, 6- or 7-membered fused ring having from 0 to 3 heteroatoms selected from the group consisting of N, O and S;

R^5 and R^6 are independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $C(O)R^a$ and CO_2R^a;

optionally, R^5 and R^6 may be combined with the nitrogen atom to form a 5-, 6- or 7-membered ring;

optionally, when X is $C(R^1)$ or when Y includes an R^1 or R^2 group, R^5 or R^6 may be combined with R^1 or R^2 to form a 5-, 6- or 7-membered fused ring containing the nitrogen atom to which R^5 or R^6 is attached;

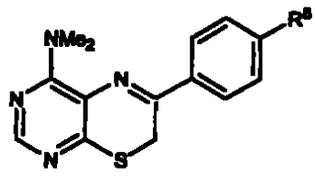
R^7 is selected from the group consisting of H, $(C_1$-$C_8)$alkyl, halo$(C_1$-$C_4)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $C(O)R^a$, OR^a and NR^aR^b;

optionally, when X is $C(R^1)$, R^7 may be combined with R^1 to form a 5-, 6- or 7-membered fused ring;

each R^a and R^b is independently selected from the group consisting of H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, fluoro$(C_1$-$C_8)$alkyl, aryl and aryl$(C_1$-$C_4)$alkyl; and

the dotted line indicates an optional bond;

with the proviso that said compound is other than



wherein R^8 is selected from the group consisting of H, NO_2, Cl, methoxy, methyl and phenyl.

28. A method in accordance with claim 27, wherein said compound is administered orally.

29. A method in accordance with claim 27, wherein said compound is administered in combination with an additional active agent.

30. A method in accordance with claim 29, wherein said additional active agent is selected from the group consisting of an antihyperlipidemic agent, a plasma HDL-raising agent, an antihypercholesterolemic agent, an HMG-CoA reductase inhibitor, an HMG-CoA synthase inhibitor, a pancreatic lipase inhibitor, SNRI, appetite suppressive agent, a PPAR modulator, a MTP inhibitor, a CETP inhibitor, a squalene epoxidase inhibitor, a squalene synthetase inhibitor, an acyl-coenzyme A cholesterol acyltransferase inhibitor, vitamin B_3, a cholesterol absorption inhibitor, a bile acid sequestrant anion exchange resin, a low density lipoprotein receptor inducer, a fibrate, probucol, vitamin B_6, vitamin B_{12}, an anti-oxidant vitamin, a β-blocker, an angiotensin II antagonist, an angiotensin converting enzyme inhibitor, a platelet aggregation inhibitor, a fibrinogen receptor antagonist, aspirin, phentiramines, β_3 adrenergic receptor agonists, sulfonylureas, biguanides, α-glucosidase inhibitors, insulin secretogogues, insulin and a hepatoprotective agent.

31. A method in accordance with claim 27, wherein said disease or condition is selected from the group consisting of diabetes, obesity and syndrome X.

32. A method in accordance with claim 27, wherein said disease or condition is obesity.

33. A method in accordance with claim 27, wherein said disease is associated with DGAT.

34. A method in accordance with claim 27, wherein said disease is mediated by DGAT.

35. A method in accordance with claim 27, wherein said compound interferes with the interaction between DGAT and a ligand.

36. A method in accordance with claim 27, wherein said subject is selected from the group consisting of human, rat, dog, cow, horse and mouse.

37. A method in accordance with claim 27, wherein said subject is human.

38. A method in accordance with claim 27, wherein X is N.

39. A method in accordance with claim 38, wherein Z is O.

40. A method in accordance with claim 39, wherein L^1 is a bond and W^1 is a substituted or unsubstituted member selected from the group consisting of benzene, pyridine, thiophene, oxazole, thiazole, benzoxazole, benzthiazole, benzofuran, benzothiophene, (C_4-C_7)cycloalkane, (C_5-C_7)cycloalkene, 1,2,3,4-tetrahydronaphthalene and indane.

41. A method in accordance with claim 40, wherein W^1 is a substituted or unsubstituted member selected from the group consisting of benzene, pyridine, thiophene, 1,2,3,4-tetrahydronaphthalene and indane.

42. A method in accordance with claim 41, wherein the subscript m is 1.

43. A method in accordance with claim 41, wherein the subscript m is 1 and L^2 is a bond.

44. A method in accordance with claim 43, wherein W^2 is a substituted or unsubstituted member selected from the group consisting of benzene, pyridine, (C_4-C_7)cycloalkane, (C_5-C_7)cycloalkene, pyrrolidine, piperidine, piperazine and morpholine.

45. A method in accordance with claim 40, wherein R^5 and R^6 are independently selected from the group consisting of H, (C_1-C_8)alkyl, $C(O)R^a$ and CO_2R^a.

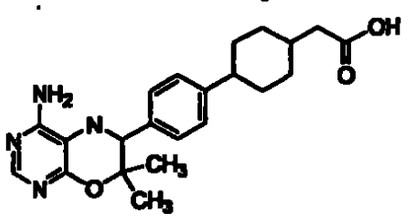
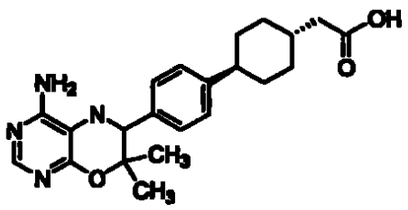
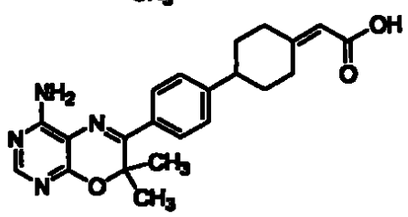
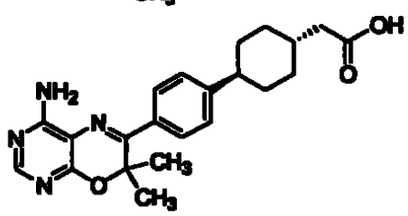
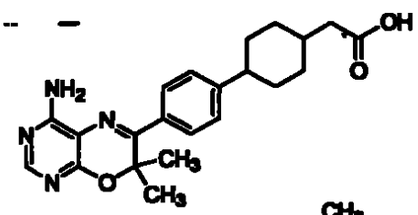
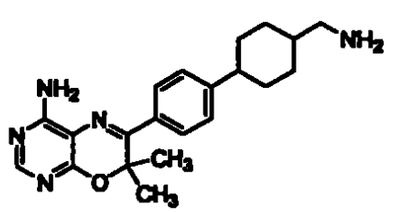
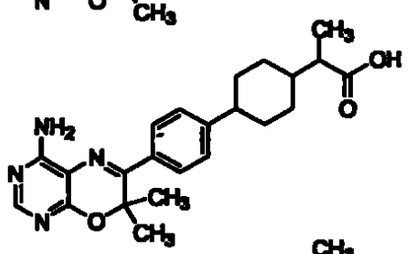
46. A method in accordance with claim 45, wherein R^5 and R^6 are independently selected from the group consisting of H and (C_1-C_8)alkyl.

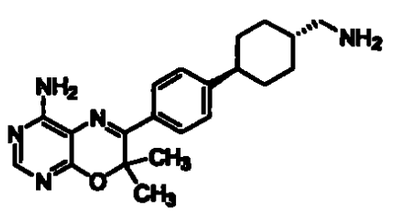
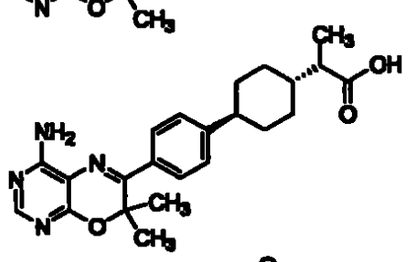
47. A method in accordance with claim 46, wherein R^3 and R^4 are independently selected from the group consisting of H and (C_1-C_8)alkyl.

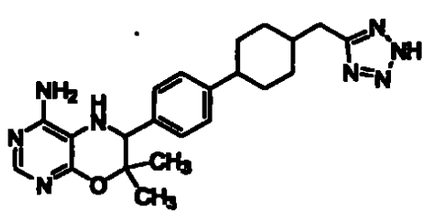
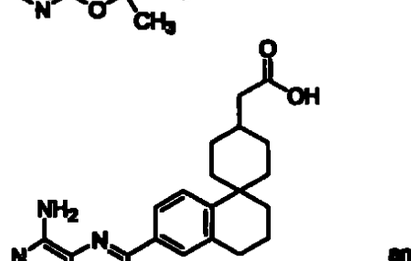
48. A method in accordance with claim 47, wherein R^7 is selected from the group consisting of H, (C_1-C_8)alkyl, halo(C_1-C_4)alkyl, OH and NR^aR^b wherein R^a and R^b are independently selected from the group consisting of H and (C_1-C_8)alkyl.

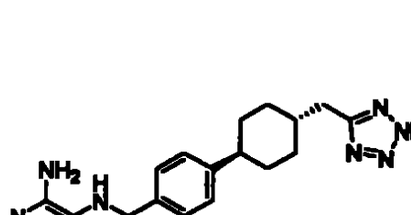
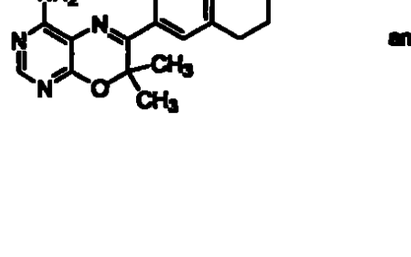
49. A method in accordance with claim 47, wherein R^7 is H, (C_1-C_8)alkyl or halo(C_1-C_4)alkyl.

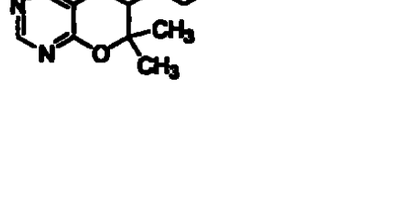
50. A compound of claim 1, selected from the group consisting of:

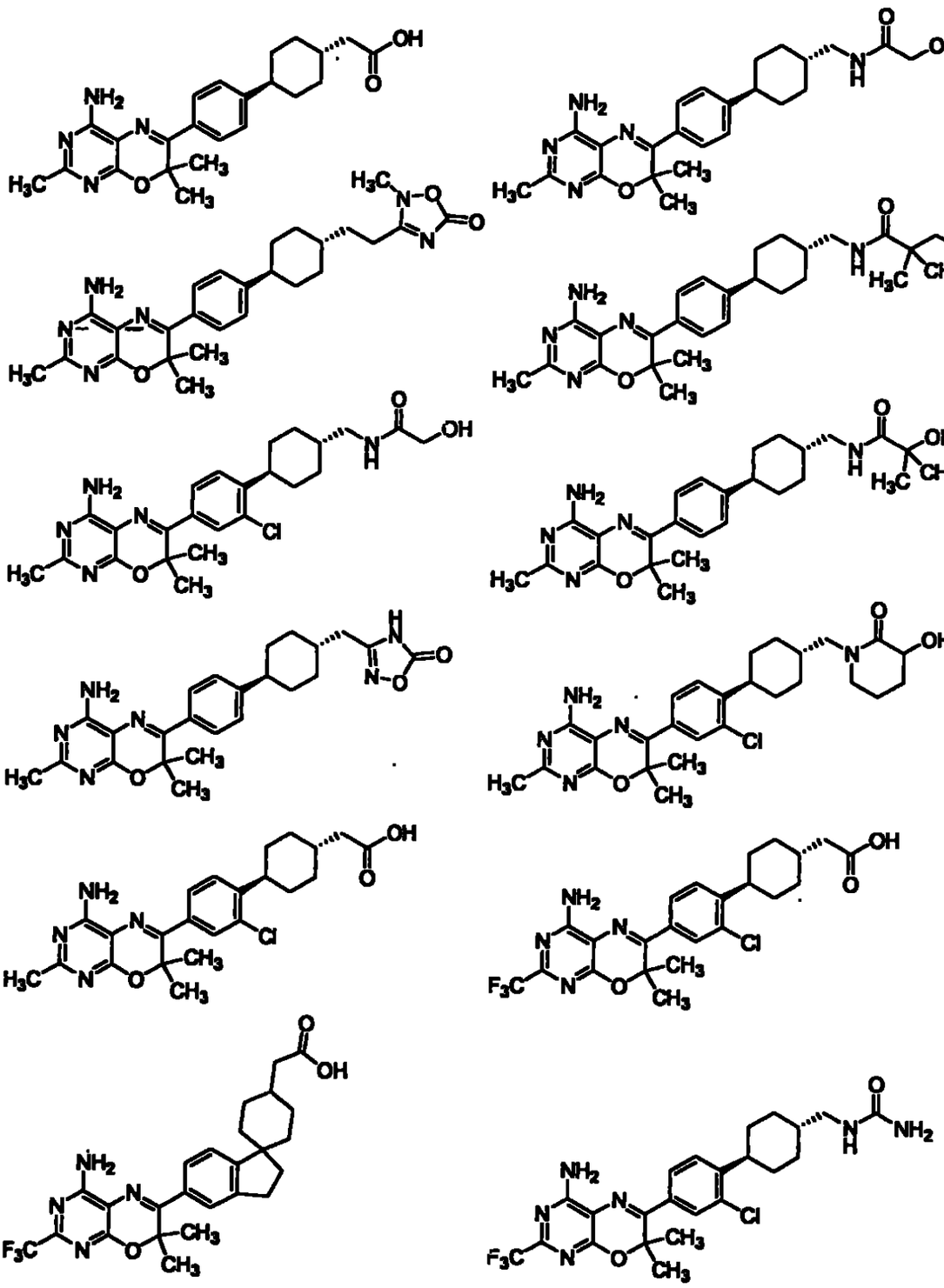



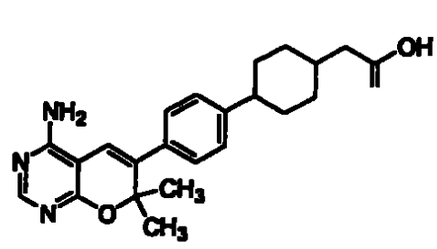



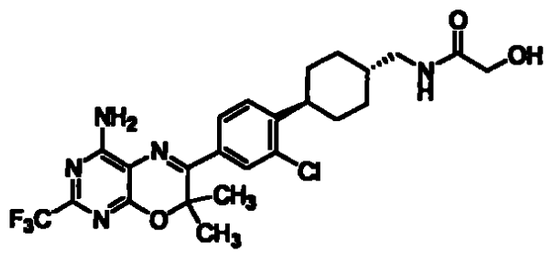


and

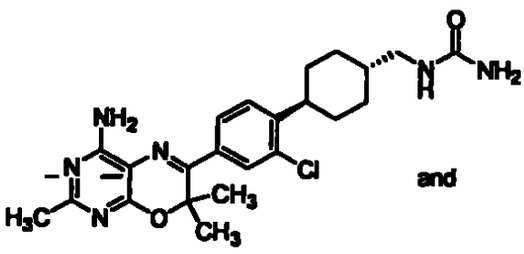


51. A compound of claim 1, selected from the group consisting of

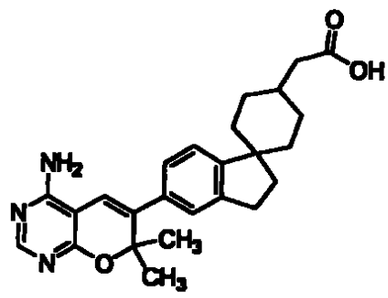








and



52. A compound having a formula selected from the group consisting of Ia, Ib, Ic, Id, Ie, If and Ig.

53. A compound having a formula selected from the group consisting of Ih, Ii, Ij and Ik.

54. A compound having a formula selected from the group consisting of Il, Im, In, Io, Ip and Iq.

55. A compound having a formula selected from the group consisting of Ir, Is, It, Iu, Iv, Iw, Ix and Iy.

HETEROCICLOS QUE CONTIENEN NITRÓGENO, BICICLICOS, FUSIONADOS

ANTECEDENTES DE LA INVENCION

Los triglicéridos representan la principal forma de energía almacenada en eucariotas. Los trastornos o desequilibrios en el metabolismo de triglicéridos están implicados en la patogénesis de, e incrementa el riesgo de obesidad, del síndrome de resistencia a la insulina y de diabetes de tipo II, enfermedades hepáticas de grasos no alcohólicos y enfermedades cardíacas coronarias (ver, Lewis, y colaboradores, Endocrine Reviews (2002) 23: 201 y Malloy y Kane, Adv. Intern. Med. (2001) 47:111). De manera adicional, la hipertrigliceridemia es a menudo una consecuencia adversa de la terapia contra el cáncer (ver, Bast, y colaboradores Cancer Medicine, 5ª. Ed., (2000) B.C. Decker, Hamilton, Ontario, CA).

Una enzima clave en la síntesis de triglicéridos es acil CoA:diacil glicerol aciltransferasa, o DGAT. La DGAT es una enzima microsómica que es ampliamente expresada en tejidos de mamíferos y que cataliza la unión de 1, 2-diacilglicerol y acil CoA graso para formar triglicéridos en el retículo endoplásmico (revisado en Chen & Farese, Trends Cardiovasc Med (2000) 10:188 y Farese, y colaboradores, Curr Opin. Lipidol (2000) 11:229).

Originalmente se pensó que la DGAT controló únicamente la catálisis de la etapa final de la acilación de diacil glicerol a triglicérido en dos rutas principales para la síntesis de triglicéridos, las rutas del fosfato de glicerol y la del monoacil glicerol. Porque los triglicéridos son considerados esenciales para la supervivencia, y se pensó que su síntesis tiene lugar a través de un mecanismo único, la inhibición de la síntesis de triglicéridos a través de la actividad de la DGAT ha sido muy inexplorada.

Actualmente se han clonado y caracterizado los genes que codifican a DGAT1 de ratón y a ARGP1 y ARGP2 homólogos humanos relacionados (Cases, y colaboradores, Proc. Natl. Acad. Sci. (1998) 95: 13018; Oelkers, y colaboradores J. Biol. Chem. (1998) 273:26765). Se ha usado el gen para DGAT1 de ratón para crear la DGAT de ratones agotados para elucidar mejor la función del gen DGAT. Inesperadamente, ratones incapaces de expresar a una enzima DGAT funcional (ratones con *Ggat-1*) son viables y aún capaces de sintetizar triglicéridos, lo que indica que los mecanismos catalíticos múltiples contribuyen a la síntesis de triglicéridos (Smith, y colaboradores, Nature Genetics (2000) 25:87). También se han identificado otras enzimas que catalizan la síntesis de triglicéridos, por ejemplo, DGAT2 y diacil glicerol transacilasa (Buhman, J.

Biol. Chem., supra y Cases, y colaboradores, J Biol Chem (2001) 276:38870).

Significativamente, ratones con D*gat-1* son resistentes a la obesidad inducida con dieta y permanecen flacos. Aún cuando alimentados con una dieta alta en grasa (21 % de grasa) los ratones con D*gat-1* mantienen pesos comparables a los de ratones alimentados con una dieta regular (4 % de grasa) y tienen un nivel corporal total de triglicéridos inferiores. La resistencia a la obesidad en ratones con D*gat-1* no es debida a la ingesta calórica decreciente, sino el resultado del consumo de energía creciente y la resistencia decreciente a la insulina y a la leptina (Smith, y colaboradores, Nature Genetics, supra; Chen y Farese, Trends Cardiovasc Med, supra; y Chen, y colaboradores, J. Clin Invest (2002) 109:1049). Adicionalmente, ratones con G*gat-1* tuvieron velocidades decrecientes de absorción de triglicéridos (Buhman, y colaboradores, J Biol Chem (2002) 277:25474). Además, del metabolismo de triglicéridos mejorado, los ratones con D*gta-1* también tienen el metabolismo de la glucosa mejorado, con niveles de insulina y de glucosa más bajos, después de una carga de glucosa, en comparación con ratones de tipo salvaje (Chen y Farese, Trends Cardiovasc Med, supra).

El hallazgo de que múltiples enzimas contribuyen a catalizar la síntesis de triglicéridos a partir de diacil glicerol, es significativo, porque presentan la oportunidad de modular un mecanismo catalítico de esta reacción bioquímica para lograr resultados terapéuticos en un individuo con efectos secundarios mínimos. Los compuestos que inhiben la conversión de diacil glicerol a triglicéridos, por ejemplo al inhibir específicamente la actividad del homólogo humano de DGAT1, se encontró el uso en concentraciones corporales descendentes y la absorción de triglicéridos para contrarrestar terapéuticamente los efectos patógenos causados por el metabolismo anormal de los triglicéridos en la obesidad, el síndrome de resistencia a la insulina y la diabetes de tipo II manifiesta, falla cardíaca congestiva y arterioesclerosis, y como una consecuencia de la terapia contra el cáncer.

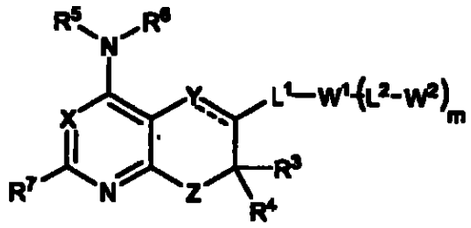
A causa del constante crecimiento imperante de la obesidad, la diabetes de tipo II, enfermedades cardíacas y el cáncer en sociedades en todo el mundo, hay una necesidad imperiosa de desarrollar nuevas terapias para tratar y prevenir efectivamente estas enfermedades Por consiguiente, hay un interés en desarrollar compuestos que pueden modular potente y específicamente un mecanismo catalizador único de la conversión enzimática de diacilglicerol a triglicéridos. Son particularmente

prometedores compuestos que inhiben específicamente la actividad catalítica de DGAT1 y sus otros homólogos de mamíferos.

BREVE SUMARIO DE LA INVENCION

La presente invención proporciona compuestos heterocíclicos que contienen nitrógeno, bicíclicos, fusionados que son útiles para tratar o prevenir condiciones y trastornos asociados con DGAT en animales, particularmente humanos.

En general, los compuestos de la presente invención son representados por la Fórmula (I):



I

o una sal, profármaco o estereoisómeros de los mismos, aceptables farmacéuticamente, en los cuales la letra X representa $C(R^1)$ o N; la letra Y representa $C(R^1)$, $C(R^2)(R^2)$, N o $N(R^2)$; y la letra Z representa O o S. El símbolo L^1, representa un enlace, (C_1-C_4)-alquileno, (C_2-C_4)-alquenileno, O o $N(R^8)C(O)$; W^1 representa un elemento substituido o no substituido seleccionado del ciclo(C_3-C_8)-

alquilo, heterociclo-(C_3-C_8)-alquilo, arilo y heteroarilo. El subíndice m es 0 o 1, indicando la presencia (m es 1) o ausencia m es cero) de la porción adicional, L^2-W^2. Aquellas modalidades en la cuales m es 1, el símbolo L^2 representa un enlace, O, (C_1-C_4)-alquileno, (C_2-C_4)-alquenileno, (C_1-C_4)-heteroalquileno o $N(R^a)C(O)$; y el símbolo W^2 representa un elemento substituido o no substituido seleccionado del ciclo-(C_3-C_8)-alquilo, heterociclo-(C_3-C_8)-alquilo, arilo y heteroarilo.

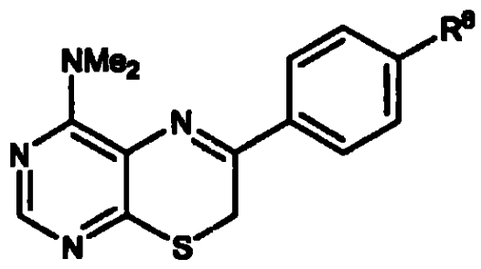
Los substituyentes restantes, R^1 hasta R^7 y R^a y R^b tienen los significados siguientes: cada R^1 es seleccionado independientemente de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, fluoro-(C_1-C_8)-alquilo, arilo, aril-(C_1-C_4)-alquilo, $C(O)R^a$ y $C(O)NR^aR^b$; cada R^2 es independientemente seleccionado de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, fluoro-(C_1-C_8)-alquilo, $C(O)R^a$, CO_2R^a, $C(O)NR^aR^b$, arilo y aril-(C_1-C_4)-alquilo; R^3 y R^4 son seleccionados independientemente de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, $C(O)R^1$, CO_2R^a, $C(O)NR^aR^b$ y (C_1-C_4)-alquileno-OR^a; R^5 y R^6 son seleccionados independientemente de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)alquinilo, $C(O)R^a$ y CO_2R^a; R^7 es seleccionado de H, (C_1-C_8)-alquilo, halo-(C_1-C_4)-alquilo, halo-(C_1-C_4)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, $C(O)R^a$, OR^a y NR^aR^b; y cada R^a y R^b es seleccionado

independientemente de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, fluoro-(C_1-C_8)-alquilo, arilo, aril-(C_1-C_4)-alquilo.

La línea punteada indica un enlace opcional. En otras modalidades opcionales, R^3 y R^4 pueden combinarse para formar un anillo espiral de 3-, 4-, 5- o 6- elementos; R^2, R^3 o R^4 pueden combinarse con W^1 para formar un anillo fusionado de 5-, 6- o 7- elementos que tiene de 0 a 3 heteroátomos seleccionados del grupo que consiste de N, y S; R^5 y R^6 pueden combinarse con el átomo de nitrógeno al cual están fijados cada uno para formar un anillo de 5-, 6- o 7- elementos; cuando X es $C(R^1)$, R^5 o R^6 pueden combinarse con R^1 para formar un anillo fusionado de 5-, 6- o 7- elementos que contienen el átomo de nitrógeno al cual están fijados R^5 o R^6; cuando X es $C(R^1)$, R^7 puede combinarse con R^1 para formar un anillo fusionado de 5-, 6- o 7- elementos; R^2 o R^1, cuando se proporcionan como parte de Y, pueden combinarse con R^5 para formar un anillo de 5- o 6- elementos con el nitrógeno al cual está fijado R^5, que poseen opcionalmente una porción oxo; y cuando m es 1 y L^2 es un enlace, un substituyente sobre W^2 puede ser combinado con un sustituyente sobre W^1 para formar un anillo de 5-, 6- o 7- elementos fusionado a W^2, en donde el anillo es saturado o no saturado y tiene 0, 1 o 2 heteroátomos seleccionados de N, O y S como elementos del

anillo.

En los compuestos anteriores de Fórmula I, el compuesto es diferentes de



en donde R^8 es H, NO_2, Cl, metoxi, metilo o fenilo.

A menos que se indique de otro modo, los compuestos proporcionados en la Fórmula anterior, incluyen todas las sales, profármacos o estereoisómeros de los mismos aceptables farmacéuticamente.

La presente invención también proporciona composiciones farmacéuticas que comprenden un compuesto de la invención y un portador o excipiente aceptable farmacéuticamente.

La presente invención también proporciona métodos para tratar o prevenir una condición o trastorno seleccionado del grupo que consiste de obesidad, diabetes, anorexia nerviosa, bulimia, caquexia, síndrome X, síndrome metabólico, resistencia a la insulina, hiperglicemia, hiperuricemia, hiperinsulinemia, hipercolesterolemia, hiperlipidemia, dislipidemia, dislipidemia mezclada, hipertrigliceridemia, enfermedad hepática grasa no

alcohólica, arterioesclerosis, falla cardíaca aguda, falla cardíaca congestiva, enfermedad de la arteria coronaria, cardiomiopatía, infarto al miocardio, angina pectoris, hipertensión, hipotensión, apoplejía, isquemia, daño por reperfusión isquémica, aneurisma, restenosis, estenosis vascular, tumores sólidos, cáncer de la piel, melanoma, linfoma, cáncer de seno, cáncer de pulmón, cáncer colonrectal, cáncer del estómago, cáncer del esófago, cáncer pancreático, cáncer de próstata, cáncer de riñón, cáncer de hígado, cáncer de vejiga, cáncer cervical, cáncer uterino, cáncer testicular y cáncer ovárico, que comprende administrar a un sujeto en necesidad del mismo una cantidad efectiva terapéuticamente de un compuesto de la invención. Por este método y los métodos proporcionados posteriormente, el compuesto de la invención será, en algunas modalidades, administrado en combinación con un segundo agente terapéutico.

La presente invención también proporciona métodos para tratar o prevenir condiciones y trastornos asociados con DGAT, que comprenden administrar a un sujeto en necesidad del mismo una cantidad efectiva terapéuticamente de un compuesto de la invención.

La presente invención proporciona adicionalmente métodos para tratar o prevenir condiciones y trastornos mediados por DGAT, que comprenden administrar a un sujeto

en necesidad del mismo, una cantidad efectiva terapéuticamente de un compuesto de la invención.

La presente invención proporciona adicionalmente métodos para modular DGAT que comprenden poner en contacto una célula con un compuesto de la invención.

DESCRIPCION DETALLADA DE LA INVENCION

Abreviaciones y Definiciones

El término "trata", "tratar" y "tratamiento" se refiere a un método de aliviar o de abrogar una enfermedad y/o auxiliar en sus síntomas.

Los términos "previene", "prevenir" y "prevención", se refiere a un método de prevenir el principio de una enfermedad y/o auxiliar en sus síntomas o proteger a un sujeto de adquirir una enfermedad. Como se usa en la presente, "previene", "prevenir" y "prevención" también incluye retardar el principio de una enfermedad y/o auxiliar en los síntomas y reducir el riesgo de un sujeto de adquirir una enfermedad.

El término "cantidad efectiva terapéuticamente" se refiere a la cantidad del compuesto que es administrada, suficiente para prevenir el desarrollo de o aliviar en alguna medida uno o más de los síntomas de la condición o trastornos que es tratado.

Como se usa en la presente, "diabetes", se refiere a

diabetes melitus de tipo I (diabetes de principio juvenil, diabetes melitus dependiente de la insulina o IDDM) o diabetes melitus de tipo II (diabetes melitus no dependiente de la insulina o NIDDM), preferiblemente diabetes de tipo II.

Como se usa en la presente, el "síndrome X" se refiere a una colección de anormalidades que incluyen hiperinsulinemia, obesidad, niveles elevados de triglicéridos, ácido úrico, fibrinógeno, partículas LDL poco densas e inhibidor del activador de plasminógeno 1 (PAI-1), y niveles decrecientes de colesterol HDL. Síndrome X quiere decir adicionalmente incluir el síndrome metabólico.

Como se usa en la presente, el término "obesidad", se refiere a la acumulación excesiva de grasa corporal. La obesidad puede tener determinantes genéticos, ambientales (por ejemplo, gastar menos energía que la que se consume) y reguladores. La obesidad incluye obesidad exógena, hiperinsulinar, hiperplásmica, hipotiroidea, hipotalámica, sintomática, infantil, corporal superior, alimentaria, hipogonádica, simple y central, adiposidad hipofisíca e hiperfagia. Trastornos metabólicos tales como hiperlipidemia y diabetes, y trastornos cardiovasculares, tales como hipertensión y enfermedad de la arteria coronaria, son asociados comúnmente con la obesidad.

El término "modula", se refiere a la habilidad de un compuesto para incrementar o disminuir la función, o actividad, de DGAT. "Modulación", como se usa en la presente en sus varias formas, se pretende que abarque el antagonismo, agonismo, antagonismo parcial y/ o agonismo parcial de la actividad asociada con DGAT. Los inhibidores de DGAT son compuestos que, por ejemplo, enlaza a, bloquea total o parcialmente la estimulación, disminuye, previene, retarda la activación, inactiva, insensibiliza, o sobre regula la transducción de señal. Los activadores de DGAT son compuestos que, por ejemplo, enlaza a, estimula, incrementa, abre, activa, facilita, mejora la activación, sensibiliza o sobre regula la transducción de señal.

El término "composición", como se usa en la presente está previsto para abarcar un producto que comprende los ingredientes específicos en las cantidades específicas, así como también cualquier producto que resulta, directa o indirectamente, de la combinación de los ingredientes específicos en las cantidades específicas. Por "aceptable farmacéuticamente" se quiere decir que el portador, diluyente o excipiente debe de ser compatible con los otros ingredientes de la formulación y no perjudicial al recipiente de los mismos.

El "sujeto" se define en la presente para incluir animales tales como mamíferos, incluyendo, pero no

limitándose a, primates (por ejemplo, humanos), vacas, ovejas, cabras, caballos, perros, gatos, conejos, ratas, ratones y los similares. En modalidades preferidas, el sujeto es un humano.

El término "DGAT" se refiere a la acil CoA:diacilglicerol aciltransferasa o una variante del mismo, a menos que se declare de otra manera. Variantes de DGAT incluyen proteínas substancialmente homólogas a DGAT nativo, es decir proteínas que tengan uno o más eliminaciones, inserciones o substituciones de aminoácidos como se encuentran de manera natural o no natural (por ejemplo, derivados, homólogos y fragmentos de DGAT). La secuencia de aminoácidos de una variante de DGAT preferiblemente es de al menos 80 % idéntica a un DGAT nativa, más preferiblemente al menos aproximadamente 90 %, y mayormente se prefiere al menos aproximadamente 95 % idéntica.

Como se usa en la presente, el término "trastorno o condición asociado con DGAT", se refiere a una condición o trastorno asociado con la actividad de DGAT inapropiada, por ejemplo, inferior que o superior a la normal y al menos responsable parcialmente a o afectada por la modulación de DGAT (por ejemplo, un inhibidor o antagonista de DGAT da como resultado algún mejoramiento en el bienestar del paciente en al menos algunos

pacientes). La actividad funcional de DGAT inapropiada debe de suscitarse como el resultado de la expresión de DGAT en células que normalmente no expresan a DGAT, expresión decreciente de DGAT o expresión de DGAT creciente. Una condición o trastorno asociado con DGAT puede incluir una condición o trastornos mediado por DGAT.

Como se usa en la presente, el término "trastorno o condición mediado por DGAT" y los similares se refieren a una condición o trastorno caracterizado por actividad de DGAT inapropiada, por ejemplo, inferior que o superior que la normal. Una condición o trastorno mediado por DGAT puede ser completa o parcialmente mediada por actividad de DGAT inapropiada. No obstante, un trastornos o condición mediada por DGAT es uno en el cual la modulación de DGAT da como resultado algún efecto sobre la condición o enfermedad prioritarios (por ejemplo, un inhibidor o antagonista de DGAT da como resultado algún mejoramiento en el bienestar del paciente en al menos algunos pacientes).

El término "alquilo", por sí mismo o como parte de otro substituyente, significa, a menos que se especifique de otra manera, una cadena recta o ramificada, o radical hidrocarburo cíclico, o combinaciones de los mismos, que estén completamente saturados, que tengan el número de átomos de carbono indicados (es decir, C_1-C_8) quiere decir

uno a ocho carbonos). Ejemplos de grupos alquilo, incluyen metilo, etilo, n-propilo, isopropilo, n-butilo, t- butilo, isobutilo, sec-butilo, ciclohexilo, (ciclohexil)-metilo, ciclopropilmetilo, homólogos e isómeros de, por ejemplo, n-pentilo, n-hexilo, n-heptilo, n-octilo y los similares.

El término "alquenilo", por sí mismo o como parte de otros substituyentes, quiere decir una cadena recta o ramificada, o radical hidrocarburo cíclico, o combinación de los mismos, que pueden ser mono- o poli-insaturado, que tiene el número de carbonos indicado (es decir, C_2-C_8 significa dos a ocho carbonos) y uno o más dobles enlaces. Ejemplos de grupos alquenilo incluyen vinilo, 2-propenilo, crotilo, 2- isopentenilo, 2- (butadienilo), 2, 4- pentadienilo, 3- (1, 4- pentadienilo) y homólogos e isómeros superiores de los mismos.

El término "alquinilo", por sí mismo o como parte de otro substituyente, significa un radical hidrocarburo ramificado o recto, o la combinación de los mismos, el cual puede ser mono- o poli-insaturado, que tiene el número de átomos de carbono indicado (es decir, C_2-C_8 significa dos a ocho carbonos) y uno o más triples enlaces. Ejemplos de grupos alquinilo incluyen etinilo, 1- y 3- propinilo, 3- butinilo y homólogos e isómeros superiores de los mismos.

El término "alquileno" por sí mismo o como parte de

otro substituyente significa un radical divalente derivado de alquilo, como se ejemplifica por $-CH_2CH_2CH_2CH_2-$. Típicamente, un grupo alquilo (o alquileno) tendrá desde 1 a 24 átomos de carbono, con aquellos grupos que tienen 10 o menos átomos de carbono que se prefieren en la presente invención. Un "alquilo inferior" o "alquileno inferior" es un grupo alquilo o alquileno de cadena más corta, que tiene generalmente ocho o menos átomos de carbono. De manera similar, "alquenileno" y "alquinileno", se refiere a versiones insaturadas de alquileno, que tiene al menos un doble enlace o un triple enlace, respectivamente. Por ejemplo, "alquenileno", quiere decir que incluye $-CH_2CH=CHCH_2-$, mientras que "alquinileno" quiere decir que incluye $-CH_2C\equiv CCH_2-$.

Los términos "alcoxi", "alquilamino" y "alquiltio" (o tioalcoxi) se usan en su sentido convencional, y se refieren a los grupos alquilo fijados en lo restante de la molécula vía un átomo de oxígeno, un grupo amino, o un átomo de azufre respectivamente.

El término "heteroalquilo" por sí mismo o en combinación con otro término, significa, a menos que se declare de otra manera, una cadena ramificada o recta estable, o radical hidrocarburo cíclico, o combinaciones de los mismos, que consisten del número establecidos de átomos de carbono y desde uno a tres heteroátomos

seleccionados del grupo que consiste de O, N, Si y S, en donde los átomos de nitrógeno y azufre pueden ser opcionalmente oxidados y el heteroátomo de nitrógeno puede ser opcionalmente cuaternizado. Los heteroátomos O, N y S pueden ser colocados en cualquier posición interior del grupo heteroalquilo. El heteroátomo Si puede ser colocado en cualquier posición del grupo heteroalquilo, incluyendo la posición en la cual el grupo alquilo está fijado a lo restante de la molécula. Los ejemplos incluyen $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $CH_2-S-CH_2-CH_3$, $-CH_2-CH_2-$, $-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, y $-CH=CH-N(CH_3)-CH_3$. Hasta dos heteroátomos pueden ser consecutivos, tales como, por ejemplo, $-CH_2-NH-OCH_3$ y $-CH_2-O-Si(CH_3)_3$.

De manera similar, el término "heteroalquileno" por sí mismo o como parte de otro substituyente significa un radical divalente derivado de heteroalquilo, como se ejemplifica por $-CH_2-CH_2-S-CH_2-CH_2-$ y $CH_2-S-CH_2-CH_2-NH-CH_2-$. Para grupos heteroalquileno, los heteroátomos pueden también ocupar ya sea uno u otro o ambas de las cadenas termini (por ejemplo, alquilenoxi, alquilendioxi, alquilenamino, alquilendiamino, y los similares). Aún adicionalmente, para grupos de enlace alquileno y heteroalquileno, no se implica ninguna orientación del grupo de enlace.

Los términos "cicloalquilo" y "heterocicloalquilo", por sí mismos o en combinación con otros términos, representan, a menos que se indique de otra manera, versiones cíclicas de "alquilo" y "heteroalquilo", respectivamente. Por consiguiente, un grupo cicloalquilo tiene el número de átomos de carbono indicados (por ejemplo, C_3-C_8 significa tres a ocho carbonos) y puede también tener uno o dos dobles enlaces. Un grupo heterocicloalquilo consiste del número de átomos de carbono indicados y desde uno a tres heteroátomos seleccionados del grupo que consiste de O, N, Si y S, y en donde los átomos de nitrógeno y de azufre pueden ser opcionalmente oxidados y el heteroátomo nitrógeno puede ser opcionalmente cuaternizado. De manera adicional, para el heterocicloalquilo, un heteroátomo puede ocupar la posición en la cual está fijado el heterociclo a lo restante de la molécula. Ejemplos de cicloalquilo incluyen ciclopentilo, ciclohexilo, 1- ciclohexenilo, 3- ciclohexenilo, cicloheptilo, y los similares. Ejemplos de heterocicloalquilo incluyen 1- (1, 2, 5, 6- tetrahidropiridilo), 1- piperidinilo, 2- piperidinilo, 3- piperidinilo, 4- morfclinilo, . 3- morfolinilo, tetrahidrofuran- 2- ilo, tetrahidrofuran- 3- ilo, tetrahidrotien-2-ilo, tetrahidrotien-3-ilo, 1- piperazinilo, 2- piperazinilo, y los similares.

Los términos "halo" y "halógeno", por sí mismos o como parte de otro substituyente, significa, a menos que se establezca de otra manera, un átomo de flúor, cloro, bromo, o yodo. De manera adicional, términos tales como "haloalquilo", quieren decir, incluir alquilo substituido con átomos de halógeno, los cuales pueden ser iguales o diferentes, en un número que varía desde uno a (2m'+1), donde m' es el número total de átomos de carbono en el grupo alquilo. Por ejemplo, el término "halo-(C_1-C_4)-alquilo" se quiere decir que incluye trifluorometilo, 2,2,2,-trifluoroetilo, 4- clorobutilo, 3- bromopropilo, y los similares. Por consiguiente, el término "haloalquilo" incluye monohaloalquilo (alquilo substituido con un átomo de halógeno) y polihaloalquilo (alquilo substituido con átomos de halógeno en un número que varía desde 2 a (2m' + 1) átomos de halógeno, donde m' es el número total de átomos de carbono en el grupo alquilo). El término "perhaloalquilo" significa, a menos que se indique de otra manera, alquilo substituido con (2m' + 1) átomos de halógeno, donde m' es el número total de átomos de carbono en el grupo alquilo. Por ejemplo el término "perhalo-(C_1-C_4)-alquilo" significa incluir trifluorometilo, pentacloroetilo, 1,1,1,-trifluoro-2-bromo-2-cloroetilo y los similares.

El término "arilo", quiere decir, a menos que se

indique de otra manera, un susbtituyente hidrocarburo, típicamente aromático, poliinsaturado que puede ser un anillo único o anillos múltiples (hasta tres anillos) los cuales están fusionados juntos o unidos covalentemente. Ejemplos no limitantes de grupos arilo incluyen fenilo, 1-naftilo, 2- naftilo, 4- bifenilo y 1, 2, 3, 4-tetrahidronaftaleno.

El término "heteroarilo" se refiere a grupos arilo (o anillos) que contienen desde uno a cuatro heteroátomos seleccionados de N, O, y S, en donde los átomos de nitrógeno y azufre son opcionalmente oxidados y los heteroátomos nitrógeno son opcionalmente cuaternizados. Un grupo heteroarilo puede estar fijado a lo restante de la molécula a través de un heteroátomo. Ejemplos no limitantes de grupos heteroarilo incluyen 1-pirrolilo, 2-pirrolilo, 3- pirrolilo, 3- pirazolilo, 2- imidazolilo, 4-imidazolilo, pirazinilo, 2- oxazolilo, 4- oxazolilo, 2-fenil- 4- oxazolilo, 3- isoxazolilo, 4- isoxazolilo, 5-isoxazolilo, 2- tiazolilo, 5- tiazolilo, 2- furilo, 3-furilo, 2- tienilo, 3- tienilo, 2- piridilo, 3- piridilo, 4- piridilo, 2- pirimidilo, 4- pirimidilo, 5-benzotiazolilo, purinilo, 2-benciimidazolilo, 5- indolilo, 1- isoquinolilo, 5- isoquinolilo, 2- quinoxalinilo, 5-quinoxalinilo, 3- quinolilo y 6- quinolilo.

Para abreviar, el término "arilo", cuando se usa en

combinación con otros términos (por ejemplo, ariloxi, ariltioxi, arilalquilo) incluye tanto los anillos arilo como los heteroarilo como se definieron anteriormente. Por consiguiente, el término "arilalquilo" quiere decir que incluye aquellos radicales en los cuales el grupo arilo está fijado a un grupo alquilo (por ejemplo, bencilo, fenetilo, piridilmetilo y los similares) incluyendo aquellos grupos alquilo en los cuales un átomo de carbono (por ejemplo, un grupo metileno) ha sido reemplazado por, por ejemplo, un átomo de oxígeno (por ejemplo, fenoximetilo, 2- piridiloximetilo, 3- (1- naftiloxi) propilo, y los similares).

Cada uno de los términos anteriores (por ejemplo, "alquilo", "heteroalquilo", "arilo", y "heteroarilo") quiere decir que incluyen tanto las formas substituidas como no substituidas del radical indicado. Los substituyentes preferidos para cada tipo de radical se proporcionan a continuación.

Los substituyentes para los radicales alquilo y heteroalquilo (así como también los grupos mencionados como alquileno, alquenilo, heteroalquileno, heteroalquenilo, alquinilo, cicloalquilo, heterocicloalquilo, cicloalquenilo y heterocicloalquenilo) pueden ser una variedad de grupos seleccionados de: -OR', =O, =NR', =N-OR', -NR'R", -SR', halógeno, -SiR'R"R''', -

$OC(O)R'$, $-C(O)R'$, $-CO_2R'$, $-CONR'R''$, $-OC(O)NR'R''$, $-NR''C(O)R'$, $-NR'-C(O)NR''R'''$, $-NR'-SO_2NR''R'''$, $-NR''CO_2R'$, $-NH-C(NH_2)=NH$, $-NR'C(NH_2)=NH$, $-NH-C(NH_2)=NR'$, $-S(O)R'$, $-SO_2R'$, $-SO_2N'R''$, $-NR''SO_2R'$, $-CN$ y $-NO_2$, en un número que varía de cero a tres, siendo particularmente preferidos aquellos grupos que tienen cero, uno o dos substituyentes. R', R'' y R''' independientemente entre sí se refieren a hidrógeno, grupos (C_1-C_6)-alquilo y heteroalquilo no substituidos, arilo no substituido, arilo substituido con uno a tres halógenos, alquilo no substituido, alcoxi o tioalcoxi, o grupos aril-(C_1-C_4)-alquilo. Cuando R' y R'' están fijados al mismos átomo de nitrógeno, pueden combinarse con el átomo de nitrógeno para formar un anillo de 5-, 6- o 5- elementos. Por ejemplo, -NR'R'' significa que incluyen 1-pirrolidinilo y 4- morfolinilo. Adicionalmente, los substituyentes anteriores pueden estar fijados al grupo alquilo (o alquileno, cicloalquilo y los similares) vía un espaciador de uno a cuatro átomos de carbono, generalmente presente como metileno o alquileno no substituido ramificado (por ejemplo $-CH_2CH_2-$ y $-CH(CH_3)(CH_2-)$, grupo alquenileno o alquinileno. Típicamente, un grupo alquilo o heteroalquilo tendrá desde cero a tres substituyentes, siendo preferidos en la presente invención los grupos que tienen dos o menos substituyentes. Más preferiblemente, un radical alquilo o

heteroalquilo será no substituido o monosubstituído. Mayormente se prefiere, un radical alquilo o heteroalquilo no substituido. De la discusión de substituyentes anterior, un experto en la materia entenderá que el término "alquilo" significa que incluye grupos tales como trihaloalquilo (por ejemplo, $-CF_3$ y $-CH_2CF_3$). Los substituyentes preferidos para los radicales alquilo y heteroalquilo son seleccionados de: -OR', =O, -NR'R", -SR', halógeno, -SiR'R"R''', -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', $-NR"CO_2R'$, $NR'SO_2NR"R'''$, -S(O)R', $-SO_2R'$, $-SO_2N'R"$, $-NR"SO_2R'$, -CN y $-NO_2$, donde R' y R" son como se definieron anteriormente. Adicionalmente, los substituyentes preferidos son seleccionados de: OR', =O, -NR'R", halógeno, -OC(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', $-NR"CO_2R'$, $-NR'-SO_2NR"R'''$, $-SO_2R'$, $-SO_2NR'R"$, $-NR"SO_2R$, -CN y $-NO_2$. De manera adicional, cada uno de los substituyentes preferidos y adicionalmente preferidos pueden ser fijados al grupo alquilo (o alquileno, cicloalquilo y los similares) vía un espaciador de uno a cuatro átomos de carbono, generalmente presente como grupos metileno o alquileno no substituido.

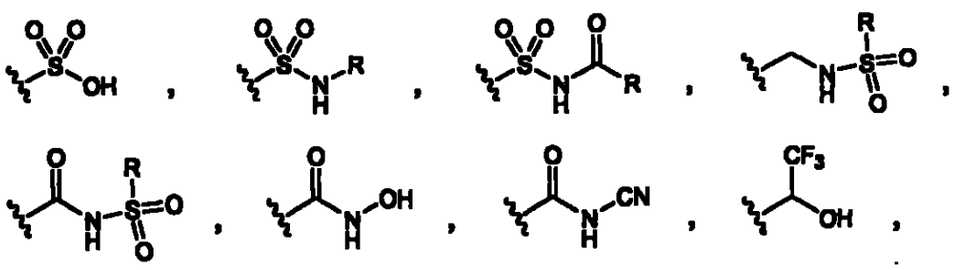
De manera similar, los substituyentes para los grupos arilo y heteroarilo son variados y seleccionados de: halógeno, -OR', -OC(O)R', -NR'R", -SR', -R', -CN, $-NO_2$, $-CO_2R'$, -CONR'R", -C(O)R', -OC(O)NR'R", -NR"C(O)R', -

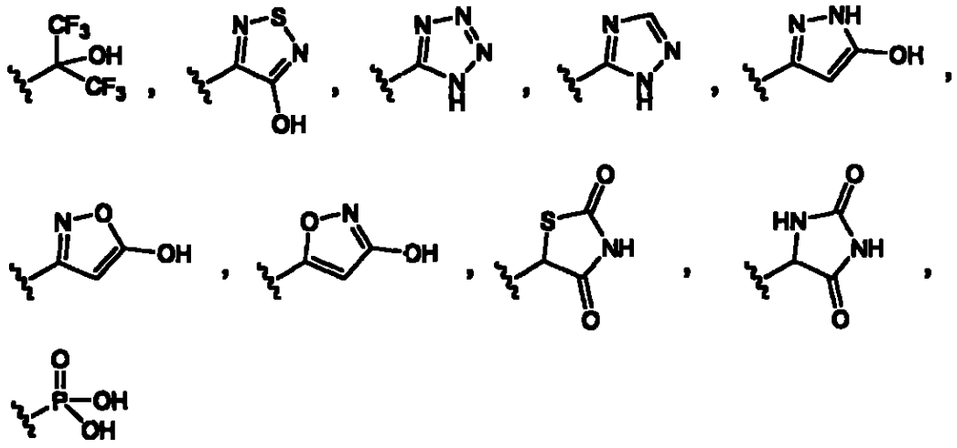
$NR''CO_2R'$, $-NR'-C(O)NR''R'''$, $-NR'-SO_2NR''R'''$, $-NH-C(NH_2)=NH$, $-NR'C(NH_2)=NH$, $-NH-C(NH_2)=NR'$, $-S(O)R'$, $-SO_2R'$, $-SO_2NR'R''$, $-NR''SO_2R'$, $-N_3$, $-CH(Ph)_2$, perfluoro-(C_1-C_4)-alcoxi y perfluoro-(C_1-C_4)-alquilo, en un número que varía de cero al número total de valencias abiertas sobre el sistema anular aromático, y donde R', R" y R''' son seleccionados independientemente de hidrógeno, (C_1-C_8)-alquilo y heteroalquilo, arilo y heteroarilo no substituido, arilo no substituido), (C_1-C_4)-alquilo y (arilo no substituido)-oxi-(C_1-C_4)-alquilo. Cuando el grupo arilo es 1, 2, 3, 4-tetrahidronaftaleno, puede ser susbtituido con un grupo (C_3-C_7)-espirocicloalquilo no substituido o substituido. El grupo (C_3-C_7)-espirocicloalquilo puede ser substituido de la misma manera comos e describió anteriormente en la presente para "cicloalquilo". Típicamente, un grupo arilo o heteroarilo será desde cero a tres substituyentes, siendo preferidos en la presente invención, los grupos que tienen dos o menos substituyentes. En una modalidad de la invención, un grupo arilo o heteroarilo será no substituido o monosubstituido. En otra modalidad, un grupo arilo o heteroarilo será no substituido. Cuando es substituido, los substituyentes anteriores pueden estar fijado al grupo arilo o heteroarilo vía un espaciador de uno a cuatro átomos de carbono, generalmente presente como grupos metileno o alquileno no substituido ramificado (por

ejemplo $-CH_2CH_2-$ y $-CH(CH_3)CH_2-$).

Los substituyentes preferidos para grupos arilo y heteroarilo son seleccionados de: halógeno, -OR', -OC(O)R', -NR'R", -SR', -R', -CN, $-NO_2$, $-CO_2R'$, -CONR'R", -C(O)R', -OC(O)NR'R", -NR"C(O)R', -S(O)R', $-SO_2R'$, $-SO_2NR'R"$, $-NR"SO_2R'$, $-N_3$, $-CH(Ph)_2$, perfluoro-(C_1-C_4)-alcoxi y perfluoro-(C_1-C_4)-alquilo, donde R' y R" son como se definieron anteriormente. Substituyentes preferidos adicionales son seleccionados de: halógeno, -OR', -OC(O)R', -NR'R", -R', -CN, $-NO_2$, $-CO_2R'$, -CONR'R", -NR"C(O)R', $-SO_2R'$, $-SO_2R'$, $-SO_2NR'R"$, $-NR"SO_2R'$, perfluoro-(C_1-C_4)-alcoxi y perfluoro-(C_1-C_4)-alquilo. Como anteriormente, estos substituyentes son fijados opcionalmente a la porción arilo o heteroarilo vía un espaciador de uno a cuatro grupos metileno.

Se comprende que el substituyente $-CO_2H$, como se usa en la presente, incluye reemplazos bioestéricos para éstos, tales como:





y los similares. Ver, por ejemplo, The practice of Medicinal Chemistry; Wemuth, C.G., Ed.; Academic Press: New York, 1996; p. 203.

Dos de los substituyentes sobre átomos adyacentes del anillo arilo o heteroarilo pueden opcionalmente ser reemplazados con un substituyentes de la fórmula -T-C(O)-$(CH_2)_q$-U-, en donde T y U son independientemente -NH-, -O-, -CH_2- o un enlace único, y q es un entero de 0 a 2. Alternativamente, dos de los substituyentes sobre átomos adyacentes del anillo arilo o heteroarilo pueden opcionalmente ser reemplazados con un substituyente de la fórmula -A-$(CH_2)_r$-B-, en donde A y B son independientemente -CH_2-, -O-, -NH-, -S-, -S(O)-, -$S(O)_2$, -$S(O)_2$NR' o un enlace único, y r es un entero de 1 a 3. Uno de los enlaces únicos del nuevo anillo así formado puede ser opcionalmente reemplazado con un doble enlace. Alternativamente, dos de los substituyentes sobre átomos

adyacentes del anillo arilo o heteroarilo pueden ser opcionalmente reemplazados con un substituyente de la fórmula $-(CH_2)_s-X-(CH_2)_t-$, donde s y t son independientemente enteros de 0 a 3, y X es -O-, -NR'-, -S-, -S(O)-, $-S(O)_2-$, o $-S(O)_2NR'-$. El substituyente R' en -NR'- y $-S(O)_2NR'-$ es seleccionado de hidrógeno o (C_1-C_6)-alquilo no substituido.

Como se usa en la presente, el término "heteroátomo" significa que incluye oxígeno (O), nitrógeno (N), azufre (S), y silicio (Si).

El término "sales aceptables farmacéuticamente" significa que incluye sales de los compuestos activos que son preparados con ácidos o bases relativamente no tóxicas, dependiendo de los substituyentes particulares encontrados en los compuestos descritos anteriormente. Cuando los compuestos de la presente invención contienen funcionalidades relativamente ácidas, las sales de adición de bases pueden ser obtenidas al poner en contacto la forma del ácido libre de dichos compuestos con una cantidad suficiente de la base deseada, ya sea pura o en un solvente inerte adecuado. Ejemplos de sales de adición de bases aceptables farmacéuticamente incluyen sales de sodio, potasio, calcio, amonio, amino orgánico, o magnesio, o una sal similar. Cuando los compuestos de la presente invención contienen funcionalidades relativamente

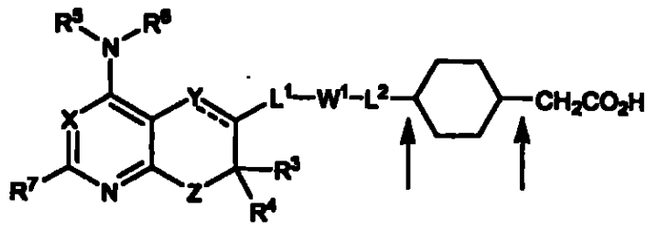
básicas, las sales de adición de ácidos pueden ser obtenidas al poner en contacto la forma de la base libre de dichos compuestos con una cantidad suficiente del ácido deseado, ya se apura o en un solvente inerte adecuado. Ejemplos de sales de adición de ácido aceptables farmacéuticamente incluyen las derivadas de ácidos inorgánicos como ácidos clorhídrico, bromhídrico, nítrico, carbónico, monohidrógenocarbónico, fosfórico, monohidrógenofosfórico, dihidrógenofosfórico, sulfúrico, monohidrógenosulfúrico, hidroiódico, o fosforoso y los similares, así como también las sales derivadas de ácidos orgánicos relativamente no tóxicos como acético, propiónico, isobutírico, maleico, malónico, benzoico, succínico, subérico, fumárico, mandélico, ftálico, bencensulfónico, p-tolilsulfónico, cítrico, tartárico, metansulfónico, y los similares. También se incluyen sales de aminoácidos tales como arginato y los similares, y sales de ácidos orgánicos como ácidos glucurónico o galacturónico y los similares (ver, por ejemplo, Berge, S. M., y colaboradores, "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). Ciertos compuestos específicos de la presente invención contienen funcionalidades tanto ácidas como básicas que permiten a los compuestos ser convertidos en sales de adición ya sea de bases o de ácidos.

Las formas neutrales de los compuestos pueden ser regeneradas al poner en contacto la sal con una base o ácido y aislando el compuesto precursor de la manera convencional. La forma precursora del compuesto difiere de las varias formas de sales en ciertas propiedades físicas, tales como solubilidad en solventes polares, pero de otra manera las sales son equivalentes a la forma precursora del compuesto para los propósitos de la presente invención. Además de las formas de sal, la presente invención proporciona compuestos que están en una forma de profármaco. Los profármacos de los compuestos descritos en la presente son aquellos compuestos que fácilmente sufren cambios químicos bajo condiciones fisiológicas para proporcionar los compuestos de la presente invención. De manera adicional, los profármacos pueden ser convertidos a los compuestos de la presente invención por medio de métodos químicos o bioquímicos en un entorno *ex vivo*. Por ejemplo, los profármacos pueden ser convertidos a los compuestos de la presente invención cuando se colocan en el depósito del parche transdérmico con una enzima o reactivo químico adecuados.

Se comprenderá que cuando un compuesto de la invención contiene uno o más átomos de carbono asimétrico (centros ópticos) o dobles enlaces, la presente invención incluye estereoisómeros individuales e isómeros

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geométricos así como también mezclas de los mismos. Por ejemplo, cuando m es 1 y W^2 es ciclo-(C_3-C_8)-alquilo substituido (por ejemplo, A.4 posterior), los isómeros 1, 4- cis y trans y los racematos de los mismos están previstos al alcance de la invención.



A.4

Ciertos compuestos de la presente invención pueden existir en formas no solvatadas así como también en formas solvatadas, incluyendo las formas hidratadas. En general, las formas solvatadas son equivalentes a las formas no solvatadas y se pretenden que sean abarcadas en el alcance de la presente invención. Ciertos compuestos de la presente invención pueden existir en múltiples formas cristalinas o amorfas. En general, todas las formas físicas son equivalentes para los usos contemplados por la presente invención y están previstos en el alcance de la presente invención.

Los compuestos de la presente invención pueden contener también proporciones no naturales de isótopos atómicos en uno o más de los átomos que constituyen dichos

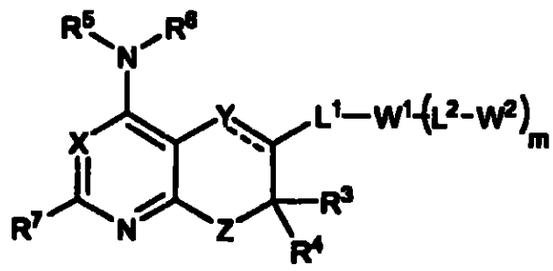
123

compuestos. Por ejemplo, los compuestos pueden ser radiomarcados con isótopos radioactivos, tales como por ejemplo tritio (^{3}H), yodo-125 (^{125}I) o carbono-14 (^{14}C). Todas las variaciones de los compuestos de la presente invención ya sea radioactivas o no, se pretende que sean abarcadas en el alcance de la presente invención.

MODALIDADES DE LA INVENCION

Compuestos

En un aspecto, la presente invención proporciona compuestos de Fórmula (I):



I

o una sal, profármaco o estereoisómeros de los mismos aceptables farmacéuticamente. En esta fórmula, la letra X representa $C(R^1)$ o N; la letra Y representa $C(R^1)$, $C(R^2)(R^2)$, N o $N(R^2)$; y la letra Z, representa O o S.

Siguiendo a los substituyentes en el núcleo heteroaromático bicíclico, el símbolo L^1, representa un enlace, (C_1-C_4)-alquileno, $(C_2-C_4$-alquenileno, O o

$N(R^a)C(O)$; y W^1 representa un elemento substituido o no substituido de ciclo-(C_3-C_3)-alquilo, heterociclo-(C_3-C_8)-alquilo, arilo o heteroarilo. El subíndice m es 0 o 1, indicando la presencia (m es 1) o ausencia (m es cero) de la porción adicional, L^2-W^2. Para las modalidades en las cuales m es 1, el símbolo L^2 representa un enlace, O, (C_1-C_4)-alquileno, (C_2-C_4) alquenileno, (C_1-C_4)-heteroalquileno o $N(R^a)C(O)$; y el símbolo W^2 representa un elemento substituido o no substituido seleccionado del ciclo-(C_3-C_8)-alquilo, heterociclo-(C_3-C_8)-alquilo, arilo y heteroarilo. Cuando m es 1 y L^2 es un enlace, un substituyente sobre W^2 puede combinarse con un substituyente sobre W^1 para formar un anillo de 5-, 6-, o 7- elementos fusionado a W^1 y espiro o fusionado a W^2, en donde el anillo es saturado o insaturado y tiene 0, 1 o 2 heteroátomos seleccionados de N, O y S como elementos del anillo. Los substituyentes para cada uno de W^1 y W^2 pueden ser seleccionados de los substituyentes proporcionados en las definiciones anteriores así como también los substituyentes citados para varias modalidades específicas posteriores.

Los substituyentes restantes, R^1 hasta R^7 y R^a y R^b tienen los significados siguientes: cada R^1 es seleccionado independientemente de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, fluoro-(C_1-C_8)-alquilo,

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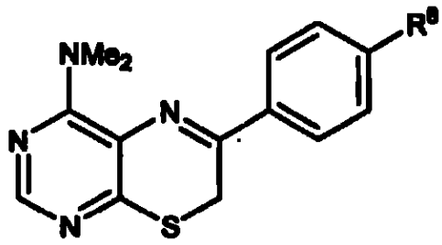
arilo, aril-(C_1-C_4)-alquilo, $C(O)R^a$ y $C(O)NR^aR^b$; cada R^2 es independientemente seleccionado de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, fluoro-(C_1-C_8)-alquilo, $C(O)R^a$, CO_2R^a, $C(O)NR^aR^b$, arilo y aril-(C_1-C_4)-alquilo; R^3 y R^4 son seleccionados independientemente de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, $C(O)R^a$, CO_2R^a, $C(O)NR^aR^b$ y (C_1-C_4)-alquileno-OR^a; R^5 y R^6 son seleccionados independientemente de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)alquinilo, $C(O)R^a$ y CO_2R^a; R^7 es seleccionado de H, (C_1-C_8)-alquilo, halo-(C_1-C_4)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, $C(O)R^a$, OR^a y NR^aR^b; y cada R^a y R^b es seleccionado independientemente de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, fluoro-(C_1-C_8)-alquilo, arilo, aril-(C_1-C_4)-alquilo.

La línea punteada indica un enlace opcional. En otras modalidades opcionales, R^3 y R^4 pueden combinarse para formar un anillo espiral de 3-, 4-, 5- o 6- elementos; R^2, R^3 o R^4 pueden combinarse con W^1 para formar un anillo fusionado de 5-, 6- o 7- elementos que tiene de 0 a 3 heteroátomos seleccionados del grupo que consiste de N, O y S; R^5 y R^6 pueden combinarse con el átomo de nitrógeno al cual están fijados cada uno para formar un anillo de 5-, 6- o 7- elementos; R^2 o R^1, cuando se proporcionan como parte de Y, pueden combinarse con R^5 para formar un anillo de 5- o de 6- elementos con el nitrógeno al cual está

fijado R^5, que posee opcionalmente una porción oxo; cuando X es $C(R^1)$, R^5 o R^6 pueden combinarse con R^1 para formar un anillo fusionado de 5-, 6- o 7- elementos que contiene el átomo de nitrógeno al cual están fijados R^5 o R^6; y cuando X es $C(R^1)$, R^7 puede combinarse con R^1 para formar un anillo fusionado de 5-, 6- o 7- elementos;

En modalidades preferidas, R^1 y R^2 son independientemente entre sí H o (C_1-C_8)-alquilo; R^3 y R^4 son independientemente entre sí H o $(C_1-C_4$-alquilo; R^5 y R^6 son cada uno H, (C_1-C_4)-alquilo o son combinados con el nitrógeno al cual están fijados cada uno para formar un anillo de 5- o 6- elementos (por ejemplo un anillo pirrolidina o piperidina); y R^7 es H, (C_1-C_8)-alquilo o halo-(C_1-C_4)-alquilo.

En los compuestos de Fórmula (I) anteriores, el compuesto es diferente de



en donde R^8 es H, NO_2, Cl, metoxi, metilo o fenilo.

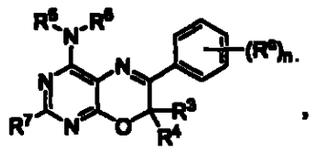
En la fórmula (I) anterior, se prefieren numerosos grupos de modalidades.

En un grupo de modalidades preferidas, X es N. Aún

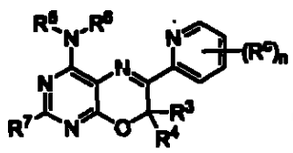
más preferiblemente, X es N y Z es O. En este grupo de modalidades, L^1 es preferiblemente un enlace y W^1 es un elemento substituido o no substituido seleccionado de benceno, piridina, tiofeno, oxazol, tiazol, benzoxazol, benzotiazol, benzofurano, benzotiofeno, (C_4-C_7)-cicloalcano, (C_5-C_7)-cicloalqueno, 1, 2, 3, 4-tetrahidronaftaleno e indano. Aún más preferiblemente, W^1 es un elemento substituido o no substituido seleccionado de benceno, piridina, tiofeno, (C_4-C_7)-cicloalcano, 1,2,3,4-tetrahidronaftaleno e indano. Para aquellas modalidades en las cuales W^1 es un benceno substituido, los substituyentes (R^c posteriores), diferentes de L^2-W^2, son preferiblemente seleccionados de halógeno (incluyendo F, Cl, Br e I), R^{c1}, OR^{c1}, $N(R^{c1})_2$, SR^{c1}, NO_2, CN, (C_1-C_8)-haloalquilo y (C_1-C_8)-haloalcoxi, en donde cada grupo R^{c1} es independientemente H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo o (C_2-C_8)-alquinilo, y opcionalmente, dos grupos R^{c1} fijados a un átomo de nitrógeno común se combinan para formar un anillo de cinco o seis elementos. De manera adicional, el benceno substituido preferiblemente tendrá desde uno a cuatro substituyentes, más preferiblemente uno o dos substituyentes y mayormente se prefiere un substituyente. Los substituyentes para cada uno de W^1 y W^2 pueden ser substituyentes proporcionados en las definiciones anteriores así como también los

substituyentes citados para varias modalidades específicas posteriores.

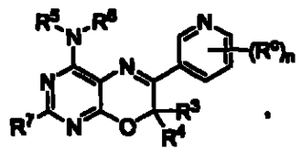
En un grupo de modalidades específicas, el subíndice m es 0 y L^1 es un enlace. Aún más preferiblemente, W^1 es seleccionado de un benceno substituido o no substituido, piridina, tiofeno, oxazol, tiazol, benzoxazol, benzotiazol, benzofurano, benzotiofeno, (C_4-C_7)-cicloalcano, (C_5-C_7)-cicloalqueno, 1, 2, 3, 4-tetrahidronaftaleno e indano. Aún más preferiblemente, W^1 es un elemento substituido o no substituido seleccionado de benceno, piridina, tiofeno, (C_4-C_7)-cicloalcano, 1, 2, 3, 4- tetrahidronaftaleno e indano. Aún adicionalmente se prefieren aquellas modalidades expuestas como Fórmulas Ia, Ib, Ic, Id, Ie, If e Ig posteriores:



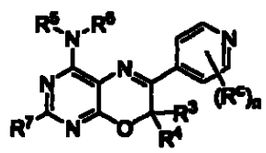
Ia



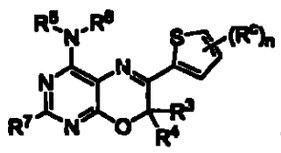
Ib



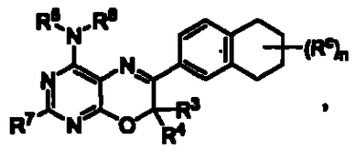
Ic



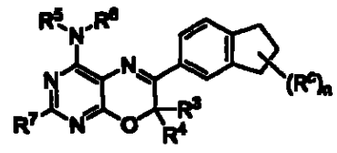
Id



Ie



If

y 

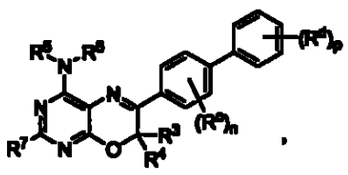
Ig

en donde el subíndice n es un entero de 0 a 4 y cada R^c representa un substituyente seleccionado independientemente de halógeno (incluyendo F, Cl, Br e I), R^{c1}, OR^{c1}, $N(R^{c1})_2$, SR^{c1}, NO_2, CN, (C_1-C_8)-haloalquilo y (C_1-C_8)-haloalcoxi, en donde cada grupo R^{c1} es independientemente H, (C_1-C_8)-alquilo, $(C_2-C_8$-alquenilo o (C_2-C_8)alquinilo y cuando R^c es $N(R^{c1})_2$, los dos gripos R^{c1} pueden combinarse para formar un anillo de cinco o de 6 elementos. Opcionalmente, para **If** e **Ig**, dos grupos R^{c1} pueden combinarse para formar un anillo espirocíclico opcionalmente substituido de 3-, 4-, 5- 6- o 7- elementos. Los substituyentes restantes tienen el significado proporcionado anteriormente con respecto a la fórmula general I.

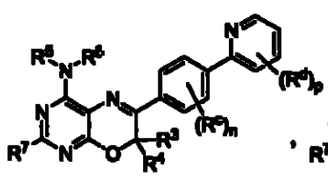
En un grupo relacionado de modalidades específicas, X es N, Z es O, L^1 es preferiblemente un enlace, W^1 es un elemento substituido o no substituido seleccionado de benceno, piridina, tiofeno, oxazol, tiazol, benzoxazol, benzotiazol, benzofurano, benzotiofeno, (C_4-C_7)-cicloalcano, (C_5-C_7)-cicloalqueno, 1, 2, 3, 4-tetrahidronaftaleno e indano, y m es 1. En este grupo de

modalidades, L^2 es preferiblemente un enlace, O o un (C_1-C_4)-heteroalquileno (por ejemplo, $-OCH_2-$, $-OCH_2CH_2-$, $-NHCH_2-$) y W^2 es un elemento substituido o no substituido seleccionado de benceno, piridina y (C_4-C_7)-cicloalcano.

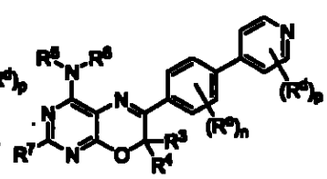
En un grupo de modalidades particularmente preferidas, el compuesto es seleccionado del grupo:



Ih

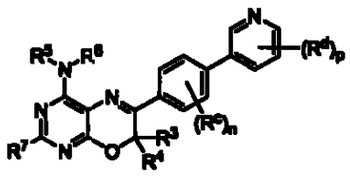


Ii



Ij

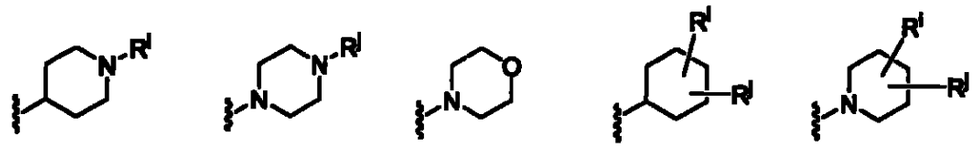
y

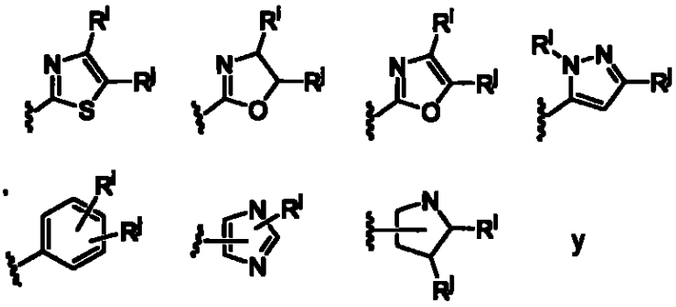


Ik

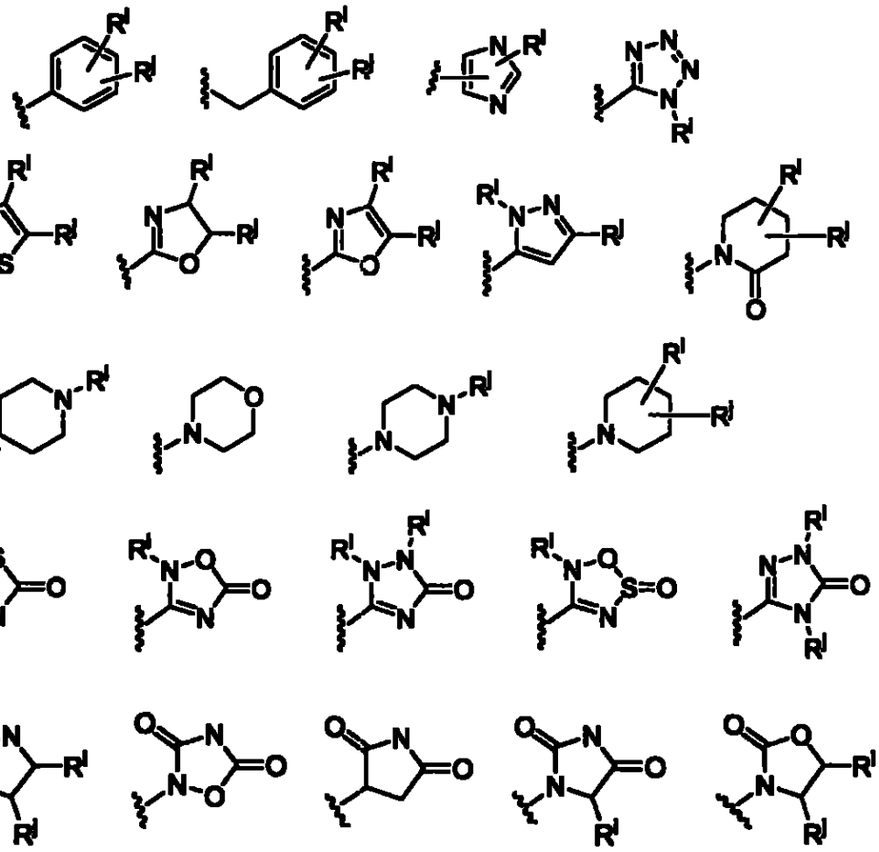
en donde el subíndice n es un entero de 0 a 4 y cada R^c representa un substituyente seleccionado independientemente de halógeno (incluyendo F, Cl, Br e I), R^{c1}, OR^{c1}, $N(R^{c1})_2$, SR^{c1}, NO_2, CN, (C_1-C_8)-haloalquilo y (C_1-C_8)-haloalcoxi, en donde cada grupo R^{c1} es independientemente H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, y opcionalmente, dos grupos R^{c1} fijados a un átomo de nitrógeno común son combinados para formar un anillo de cinco- o de seis- elementos. Adicionalmente, el subíndice p es un entero de 0 a 4, más preferiblemente 0, 1 o 2, y cada R^d es un substituyente seleccionado

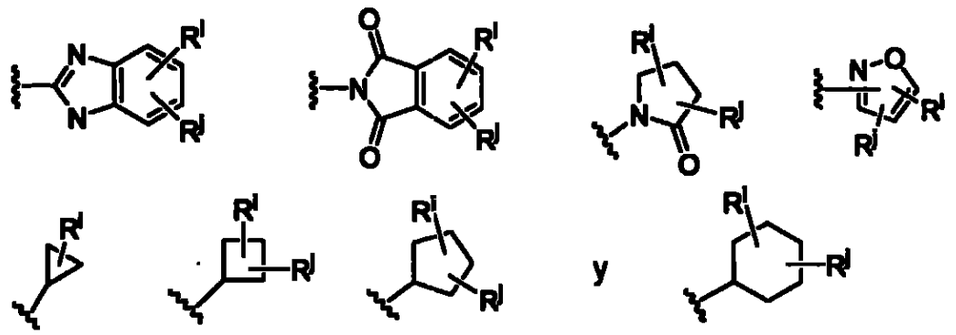
independientemente de halógeno (incluyendo F, Cl, Br e I), R^{d1}, OR^{d1}, $N(R^{d1})_2$, $-(CH_2)-S(O)_uR^c$, NO_2, CN, (C_1-C_8)-haloalquilo, (C_1-C_8)haloalcoxi, aril-(C_1-C_4)-alquilo, heteroaril-(C_1-C_4)-alquilo, $-CH(R^f)-CO_2R^e$, $-C(R^f)_2-CO_2R^c$, $-(CH_2)_t-CO_2R^c$, $-(CH_2)_t-C(O)R^c$, $-(CH_2)_t-C(O)NR^eR^f$, $-(CH_2)_t-NHSO_2R^e$, $-(CH_2)_t-SO_2NR^eR^f$, $-(CH_2)_t-NR^eR^f$, $-(CH_2)_t-OR^e$, $-(CH_2)_t-NHSO_2NHCO_2R^e$, $-(CH_2)_t-NHSO_2NR^eR^f$, $-(CH_2)_t-CONHSO_2R^e$, $-(CH_2)_t-W^3$, $-(CH_2)_t-NHCO_2R^e$, $-(CH_2)_t-NR^fCOR^e$, $-(CH_2)_t-NHCONR^eR^f$ y $-(CH_2)_t-NHCO-(CH_2)_t-OCOR^e$, en donde el subíndice t en cada caso es un entero de 0 a 8, el subíndice u es un entero de 0 a 2, R^{d1} es seleccionado de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo y (C_3-C_8)-cicloalquilo, en donde la porción alifática es opcionalmente substituida con OH, CO_2H, NH_2, $CONH_2$, fenilo, halógeno, halo-(C_1-C_4)-alquilo y CO_2R^8, y opcionalmente dos grupos R^{d1} fijados a un nitrógeno común se combinan para formar un anillo de cinco o de seis elementos, y en donde cada R^e y R^f es independientemente H o (C_1-C_8)-alquilo o cuando están fijados a un nitrógeno común se combinan para formar un anillo de 5- o de 6- elementos, o son opcionalmente seleccionados de





y en donde cualquier porción alquilo de R^e y R^f es opcionalmente substituida con un elemento seleccionado de OH, $COOH_4$, NH_2, $CONH_2$, fenilo, dialquilamino y $COOHR^g$ en donde R^g es un (C_1-C_4)-alquilo; y W^3 es seleccionado de:



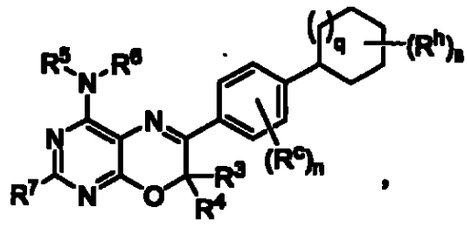


En donde cada R^i y cada R^j es seleccionado independientemente de H, OH, COOH, halógeno, halo-(C_1-C_4)-alquilo, hidroxi-(C_1-C_4)-alquilo, (C_1-C_6)-alquilo, (C_1-C_6)-alcoxi, (C_1-C_6)-alcoxi-(C_1-C_4)-alquilo y COO-(C_1-C_4)-alquilo, en donde las porciones alifáticas son no substituidas u opcionalmente substituidas con halógeno.

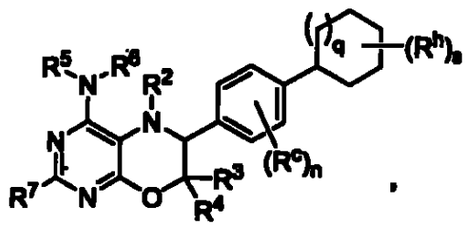
En algunas modalidades, los substituyentes R^d son seleccionados de halógeno (incluyendo F, Cl, Br e I), R^{d1}, OR^{d1}, $N(R^{d1})_2$, SR^{d1}, NO_2, CN, (C_1-C_8)-haloalquilo, (C_1-C_8)-haloalcoxi, aril-(C_1-C_4)-alquilo, heteroaril-(C_1-C_4)-alquilo, (C_1-C_8)-alquileno-CO_2R^e, $C(O)R^e$, CO_2R^e, $-CH_2-CO_2R^e$, $-CH(R^f)-CO_2R^e$, $-C(R^f)_2-CO_2R^e$, $-CH_2CH_2CO_2R^e$, $-C(O)NR^eR^f$, $-CH_2C(O)NR^eR^f$, $-CH_2CH_2CONR^eR^f$, $-NHSO_2R^e$, $-CH_2NHSO_2R^e$, $-CH_2CH_2NHSO_2R^e$, $-CH_2SO_2NR^eR^f$, $-CH_2CH_2SO_2NR^eR^f$, $-CH_2OH$, $-CH_2NR^eR^f$, CH_2CH_2OH, $-CH_2C(CH_3)_2OH$, $-CH_2-W^3$, y $-C(O)CO_2R^t$, en donde cada R^{d1}, R^e, R^f y W^3 tienen el significado proporcionado anteriormente, con respecto a las Fórmulas **Ih**, **Ii**, **Ij** e **Ik**, y los substituyentes restantes tienen los significados proporcionados anteriormente con respecto a

la fórmula general I.

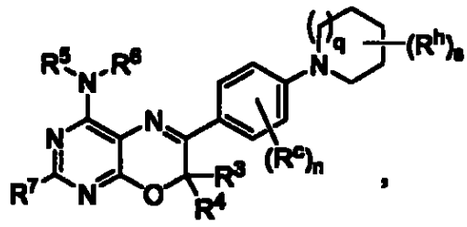
En aún otras modalidades preferidas, el compuesto tiene una fórmula seleccionada de:



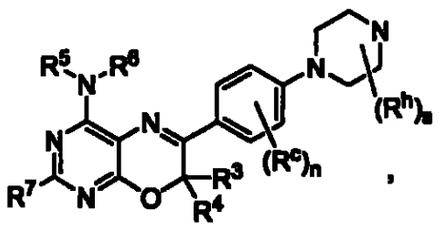
II



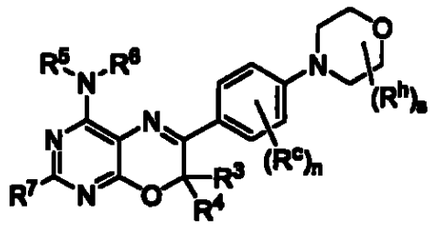
Im



In

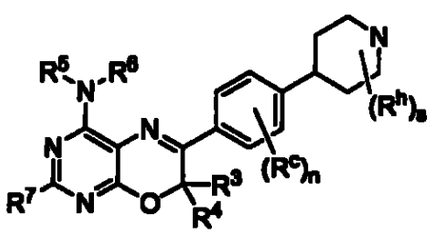


Io



Ip

y

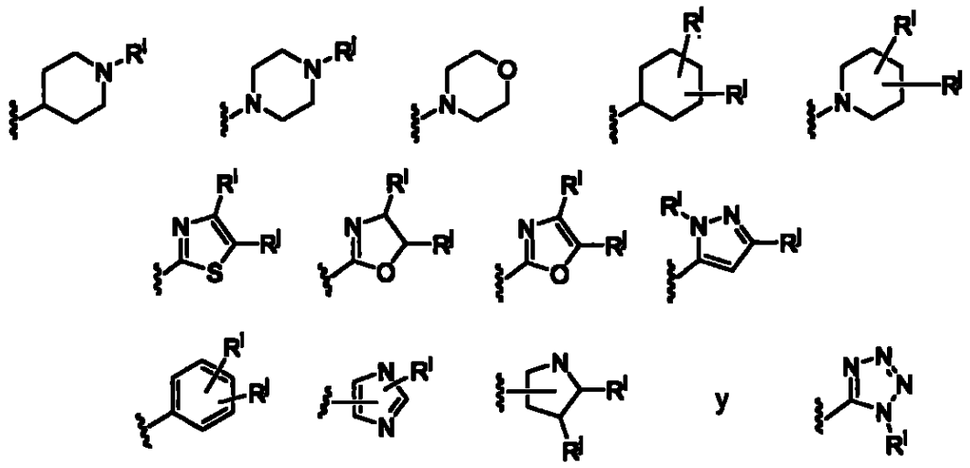


Iq

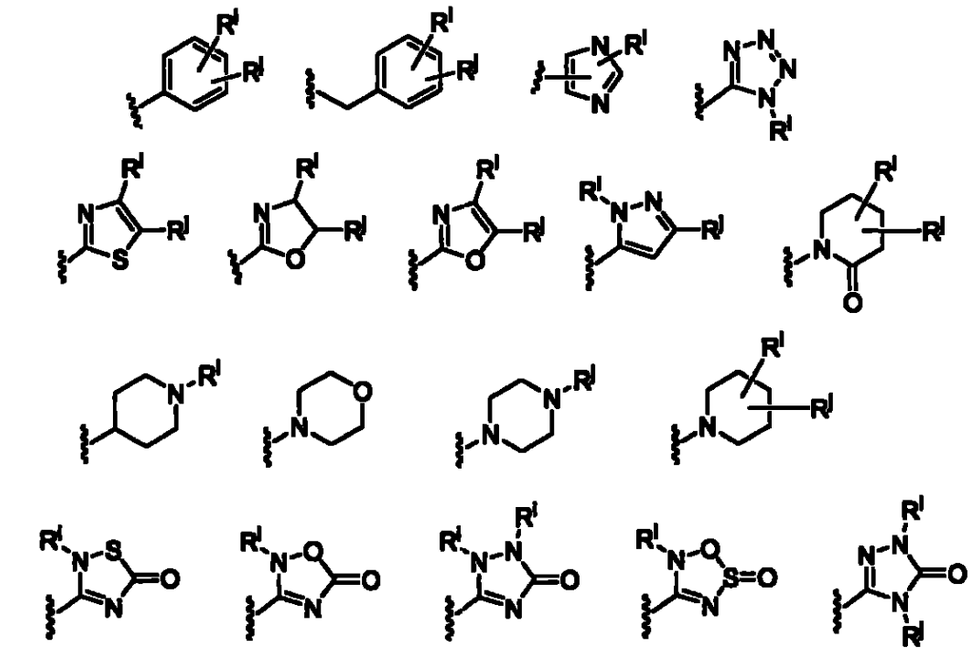
en donde cada uno de R^2, R^3, R^4, R^5, R^6, R^7 y R^c, así como también el subíndice n tienen los significados proporcionados anteriormente con respecto a las Fórmulas Ia-Ik. El subíndice q es un entero de 0 a 3, más preferiblemente, 0 o 1. El subíndice s es un entero de 0 a

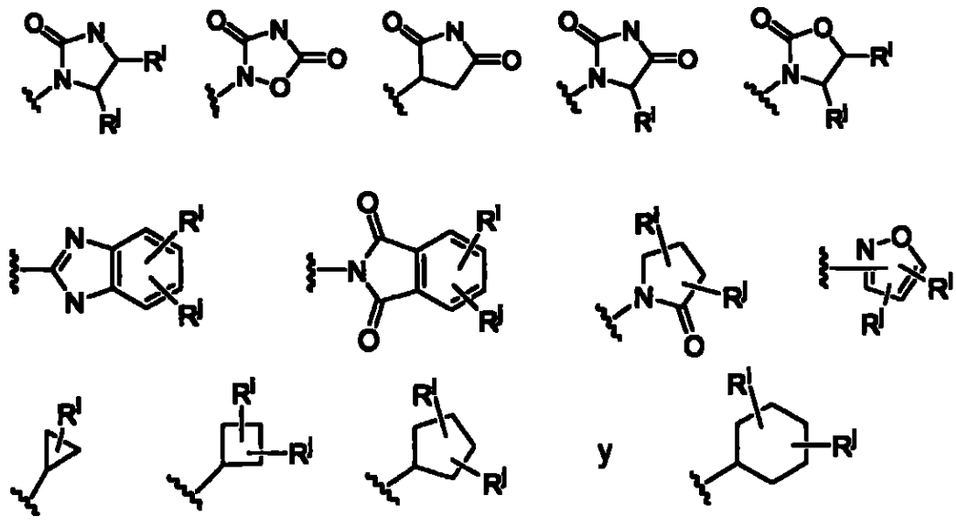
4, más preferiblemente 0, 1 o 2, y cada R^h es un substituyente seleccionado independientemente de oxo, halógeno (incluyendo F, Cl, Br, e I), R^{h1}, $N(R^{h1})$, $N(R^{h1})_2$, $-(CH_2)_t-S(O)_uR^e$, NO_2, CN, (C_1-C_8)-haloalquilo, (C_1-C_8)-haloalcoxi, aril-(C_1-C_4)-alquilo, heteroaril-(C_1-C_4)-alquilo, $-CH(R^f)-CO^2R^e$, $-C(R^f)_2-CO_2R^e$, $-C(O)CO_2R^e$, $=CH-CONR^eR^f$, $=CH-CO_2R^e$, $-(CH_2)_tCO_2R^e$, $-(CH_2)_t-C(O)NR^eR^f$, $-(CH_2)_t-NHSO_2R^e$, $-(CH_2)_t-SO_2NR^eR^f$, $-(CH_2)_t-NR^eR^f$, $-(CH_2)_t-OR^e$, $-(CH_2)_t-NHSO_2NHCO_2R^e$, $-(CH_2)_t-NHSO_2NR^eR^f$, $-(CH_2)_t-CONHSO_2R^e$, $-(CH_2)_t-W^3$, $-(CH_2)_t-NHCO_2R^e$, $-(CH_2)_t-NR^fCOR^e$, $-(CH_2)_t-NHCONR^eR^f$ y $-(CH_2)_t-NHCO-(CH_2)_t-OCOR^e$, en donde el subíndice t en cada caso es un entero de 0 a 8, el subíndice u es un entero de 0 a 2, R^{h1} es seleccionado de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo y (C_3-C_8)-cicloalquilo, en donde la porción alifática es opcionalmente substituida con OH, CO_2H, NH_2, $CONH_2$, fenilo, halógeno, halo-(C_1-C_4)-alquilo y CO_2R^g, y opcionalmente dos grupos R^{h1} fijados a un nitrógeno común son combinados para formar un anillo de cinco o de seis elementos, o un grupo R^h y uno R^{h1} pueden combinarse para formar un anillo espiro o fusionado de 3-, 4-, 5-, o 6- elementos que tienen de cero a dos heteroátomos seleccionados de N, O y S; y en donde cada R^e y R^f es independientemente H o (C_1-C_8)-alquilo o cuando están fijados a un átomo de nitrógeno común se combinan para formar un anillo de 5- o de 6- elementos, o son

seleccionados opcionalmente de:



y en donde cualquier porción alquilo de R^e y R^f es opcionalmente substituida con un elemento seleccionado de OH, COOH, NH_2, $CONH_2$, fenilo, dialquilamino y $COOR^g$, en donde R^g es un (C_1-C_4)-alquilo; y W^3 es seleccionado de:





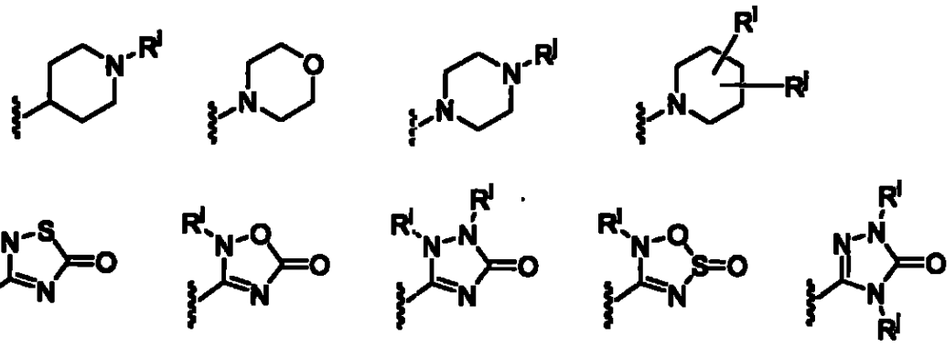
en donde cada R^i y cada R^j es seleccionado independientemente de H, OH, COOH, halógeno, halo-(C_1-C_4)-alquilo, hidroxi-(C_1-C_4)-alquilo, (C_1-C_6)-alquilo, (C_1-C_6)-alcoxi, (C_1-C_6)-alcoxi-(C_1-C_4)-alquilo y COO-(C_1-C_4)-alquilo, en donde las porciones alifáticas son no substituidas u opcionalmente substituidas con halógeno.

En algunas modalidades, los substituyentes R^h son seleccionados de oxo, halógeno (incluyendo F, Cl, Br e I), R^{hl}, OR^{hl}, $N(R^{hl})_2$, SR^{hl}, NO_2, CN, (C_1-C_8)-haloalquilo, (C_1-C_8)-haloalcoxi, aril-(C_1-C_4)-alquilo, heteroaril-(C_1-C_4)-alquilo, (C_1-C_8)-alquileno-CO_2R^e, $C(O)R^e$, CO_2R^e, $=CH-CONR^eR^f$, $=CH-CO_2R^e$, $-CH_2-CO_2R^e$, $-CH(R^f)-CO_2R^e$, $-C(R^f)_2-CO_2R^e$, $-CH_2CH_2CO_2R^e$, $-C(O)NR^eR^f$, $-CH_2C(O)NR^eR^f$, $-CH_2CH_2CONR^eR^f$, $-NHSO_2R^e$, $-CH_2NHSO_2R^e$, $-CH_2CH_2NHSO_2R^e$, $-CH_2SO_2NR^eR^f$, $-CH_2CH_2SO_2NR^eR^f$, $-CH_2OH$, $-CH_2NR^eR^f$, CH_2CH_2OH, $-CH_2C(CH_3)_2OH$, $-CH_2-W^3$, $-CH_2CH_2-W^3$ y $-C(O)CO_2R^e$, en donde R^{hl}, R^e, R^f y W^3

tienen los significados proporcionados anteriormente, con respecto a las Fórmulas II, Im, In, Io, Ip y Iq, y los substituyentes restantes tienen los significados proporcionados anteriormente con respecto a la Fórmula General I.

En algunas modalidades de cada una de las Fórmulas Ia hasta Iq, R^2 (cuando está presente) es H o un (C_1-C_8)-alquilo; R^3 y R^4 son independientemente entre sí H, (C_1-C_4)-alquilo o se combinan para formar una anillo espirocíclico de 3-, 4-, 5- o 6- elementos; R^5 y R^6 son cada uno H, (C_1-C_4)-alquilo o se combinan con el nitrógeno al caula cada uno está fijado para formar un anillo de 5- o de 6- elementos (por ejemplo, un anillo pirrolidina o piperidina); y R^7 es H, (C_1-C_8)-alquilo o halo-(C_1-C_4)-alquilo. Aún adicionalmente se prefieren las modalidades en las cuales el subíndice n es 0, q es 1 y s es 1. En un grupo particularmente preferido de modalidades, el compuesto tiene la Fórmula II, Im o In, y R^h representa un substituyente que tiene la fórmula $C(O)R^e$, CO_2R^e, $=CH-CO_2R^e$, $-CH_2-CO_2R^e$, $-CH_2NHCOR^e$, $-CH(R^f)-CO_2R^e$, $-C(R^f)_2CO_2R^e$, $-CH_2CH_2CO_2R^e$, $-C(O)NR^eR^f$, $=CH-CONR^eR^f$, $-CH_2C(O)NR^eR^f$, $-CH_2CH_2C(O)NR^eR^f$, $-CH_2CH_2NHCO_2R^e$, $-CH_2NHCO_2R^e$, $-NHSO_2R^e$, $-CH_2NHSO_2R^e$, $-CH_2CH_2NHSO_2R^e$, $-CH_2SO_2NR^eR^f$, $-CH_2CH_2SO_2NR^eR^f$, $-CH_2OH$, $-CH_2NR^eR^f$, $-CH_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2-W^3$, $-CH_2CH_2-W^3$, $-C(O)CO_2R^e$ o $-CH_2-C(CF_3)_2-OH$. En un grupo adicional de

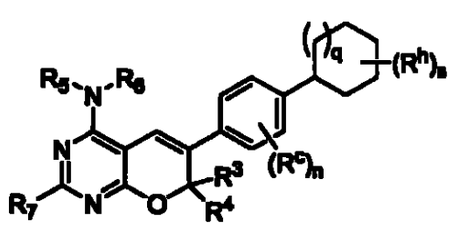
modalidades preferidas, los compuestos tienen la Fórmula II en la cual R^3 y R^4 son independientemente H o (C_1-C_4)-alquilo no substituido; R_5 y R_6 son independientemente H o (C_1-C_4)-alquilo no substituido; R^7 es seleccionado de H, $((C_1-C_4)$-alquilo no substituido o halo-(C_1-C_4)-alquilo; el subíndice n es 0, 1 o 2 y R^c es seleccionado de flúor, cloro, bromo, ciano, metilo, trifluorometilo y nitro; R^h es seleccionado de CO_2R^e, $=CH-CO_2R^e$, $-CH_2CO_2R^e$, $-CH_2NHCOR^e$, $-CH(R^f)-CO_2R^e$, $-C(R^f)_2-CO_2R^e$, $-CH_2CH_2CO_2R^t$, $-C(O)NR^eR^f$, $=CH-CONR^eR^f$, $-CH_2C(O)NR^eR^f$, $-CH_2CH_2C(O)NR^eR^f$, $-CH_2CH_2NHCO_2R^e$, $-CH_2NHCO_2R^e$, $-CH_2NR^eR^f$, $-CH_2-W^3$ y $-CH_2CH_2-W^3$; en donde cada R^c y R^f es H o (C_1-C_4)-alquilo opcionalmente substituido con un elemento seleccionado de OH, COOH, NH_2, $CONH_2$, fenilo, dialquilamino y $COOR^8$, en donde R^8 es un $(C_1-C_4$-alquilo; y en donde W^3 es seleccionado de:



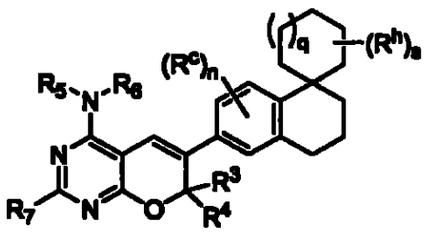
en donde R^i y R^j son independientemente entre sí seleccionados de H y (C_1-C_4)-alquilo.

En aún otros grupos de modalidades preferidas, los compuestos están representados por las Fórmulas Ir hasta

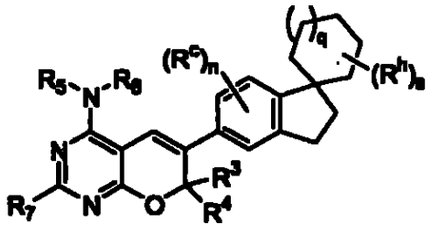
Iy.



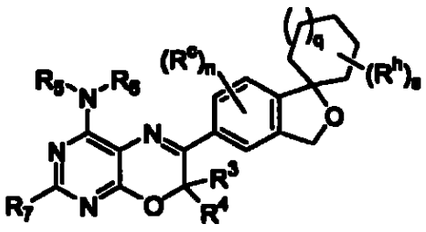
Ir



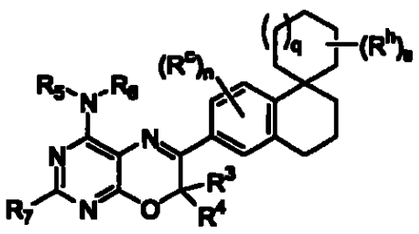
Is



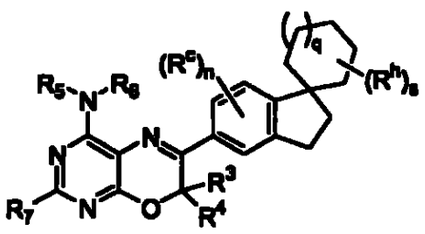
It



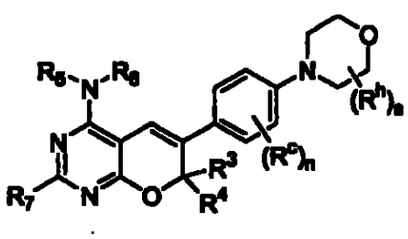
Iu



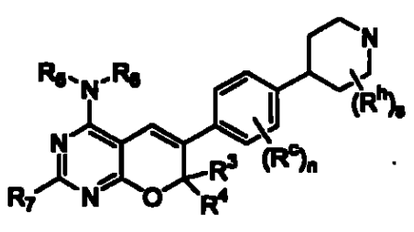
Iv



Iw



Ix



Iy

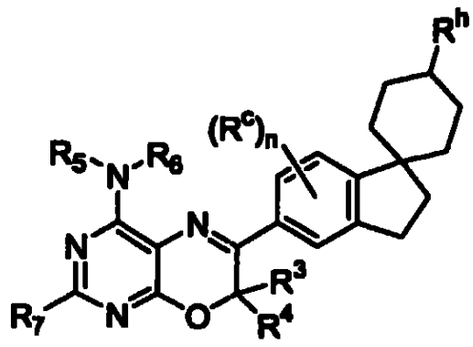
en donde cada uno de R^3, R^4, R^5, R^6, R^7 y R^c, así como también el subíndice n tienen el significado proporcionado anteriormente con respecto a las Fórmulas **Ia-Ik**. El subíndice q es un entero de 0 a 3, más preferiblemente, 0

o 1. El subíndice s es un entero de 0 a 4, más preferiblemente 0, 1 o 2, y cada R^h es un substituyente seleccionado independientemente de los grupos proporcionados anteriormente para las Fórmulas **II**, **Im**, **Io**, **Ip** e **Iq**. Grupos preferidos para R^h son aquellos proporcionados anteriormente como grupos preferidos para las Fórmulas **II**, **Im**, **In**, **Io**, **Ip** e **Iq**.

En modalidades preferidas, R^3 y R^4 son independientemente entre sí H, (C_1-C_4)-alquilo o se combinan para formar un anillo espirocíclico de 3-, 4-, 5- o 6- elementos; R^5 y R^6 son cada uno H, (C_1-C_4)-alquilo o se combinan con el nitrógeno al cual está fijado cada uno para formar un anillo de 5- o de 6- elementos (por ejemplo un anillo pirrolidina o piperidina); y R^7 es H, (C_1-C_8)-alquilo o halo-(C_1-C_4)-alquilo. Aún adicionalmente se prefieren aquellas modalidades en las cuales el subíndice n es 0, q es 1 y s es 1. En un grupo particularmente preferido de modalidades, R^h, representa un substituyente que tiene la fórmula $C(O)R^e$, CO_2R^e, $=CH-CO_2R^e$, $-CH_2-CO_2R^e$, $-CH(R^f)-CO_2R^e$, $-C(R^f)_2-CO_2R^e$, $-CH_2CH_2CO_2R^e$, $-C(O)NR^eR^f$, $=CH-CONR^eR^f$, $-CH_2C(O)NR^eR^f$, $-CH_2CH_2C(O)NR^eR^f$, $-CH_2CH_2NHCO_2R^e$, $-CH_2NHCO_2R^e$, $-NHSO_2R^e$, $-CH_2NHSO_2R^e$, $-CH_2CH_2NHSO_2R^e$, $-CH_2SO_2NR^eR^f$, $-CH_2CH_2SO_2NR^eR^f$, $-CH_2OH$, $-CH_2NR^eR^f$, $-CH_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-CH_2-W^3$, $-CH_2CH_2-W^3$, $-C(O)CO_2R^e$ o $-CH_2-C(O)(CF_3)_2-OH$, en donde cada R^e, Rf y W^3 es como se

describió anteriormente.

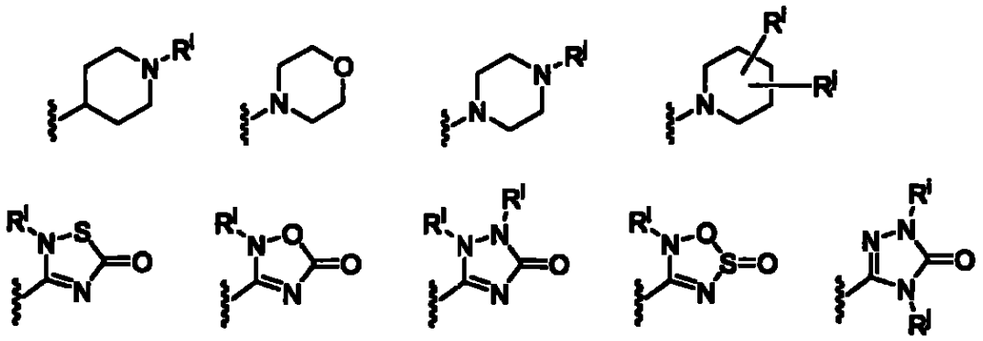
En un grupo particularmente preferido de modalidades, los compuestos tienen la fórmula **Iw.4** en donde los substituyentes tienen el significado proporcionado anteriormente con respecto a la Fórmula General I y preferiblemente son seleccionados de de los grupos preferidos proporcionados con respecto a la Fórmula **Ir** hasta **Iy**.



Iw.4

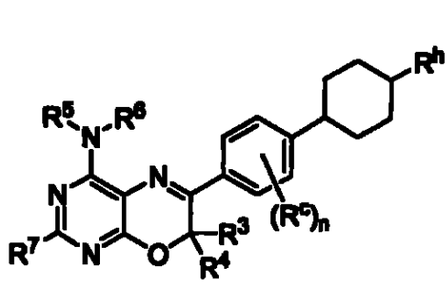
Más preferiblemente, los compuestos de Fórmula **Iw.4** son aquellos en los cuales R^3 y R^4 son independientemente H o (C_1-C_4)-alquilo no substituido; R^5 y R^6 son independientemente H o (C_1-C_4)-alquilo no substituido; R^7 es seleccionado de H, (C_1-C_4)-alquilo no substituido o halo-(C_1-C_4)-alquilo; el subíndice n es 0, 1 o 2 y R^c es seleccionado de flúor, cloro, bromo, ciano, metilo, trifluorometilo y nitro; R^h es seleccionado de CO_2R^e, $=CH-CO_2R^e$, $-CH_2-CO_2R^e$, $-CH_2NHCOR^e$, $-CH(R^f)-CO_2R^e$, $-C(R^f)_2-CO_2R^e$, $-CH_2CH_2CO_2R^e$, $-C(O)NR^eR^f$, $=CH-CONR^eR^f$, $-CH_2C(O)NR^eR^f$, -

$CH_2CH_2C(O)NR^eR^f$, $-CH_2CH_2NHCO_2R^e$, $-CH_2NHCO_2R^e$, $-CH_2NR^eR^f$, $-CH_2-W^3$ y $-CH_2CH_2-W^3$; en donde cada R^e y R^f es H o (C_1-C_4)-alquilo opcionalmente substituido con un elemento seleccionado de OH, COOH, NH_2, $CONH_2$, fenilo, dialquilamino y $COOR^g$ en donde R^g es un (C_1-C_4)-alquilo; y en donde W^3 es seleccionado de:

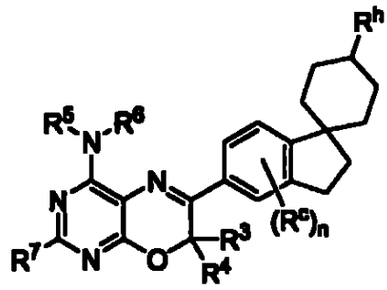


en donde R^i y R^j son independientemente entre sí, seleccionados de H y (C_1-C_4)-alquilo no substituido.

En otros grupos de modalidades particularmente preferidas, los compuestos son representados por las Fórmulas **II.4** y **Ig.4**:



y



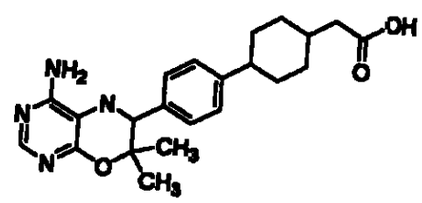
II.4 **Ig.4**

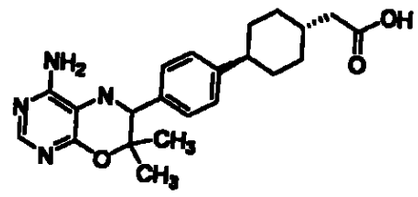
en donde cada uno de los substituyentes tiene los significados y los grupos preferidos que se proporcionaron

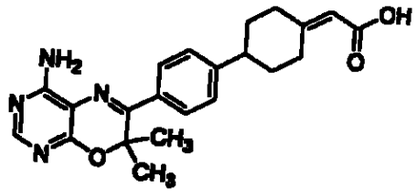
anteriormente para las Fórmulas Ir hasta Iy.

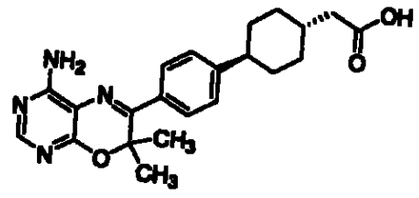
Los compuestos más preferidos de la presente invención son aquellos que se proporcionaron en los ejemplos posteriores y se ejemplifican en las Tablas 1-10.

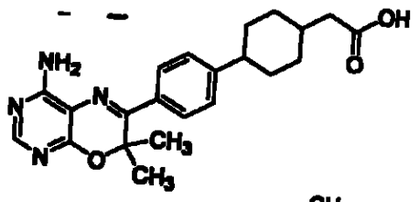
En un grupo de modalidades particularmente preferido, los compuestos son seleccionados de:

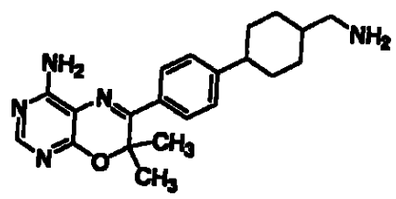


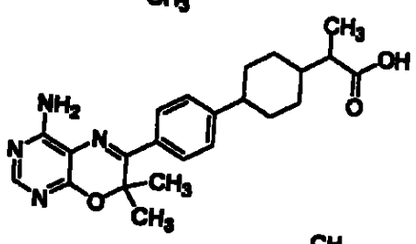


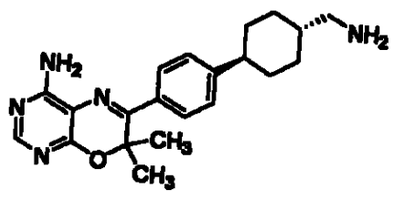


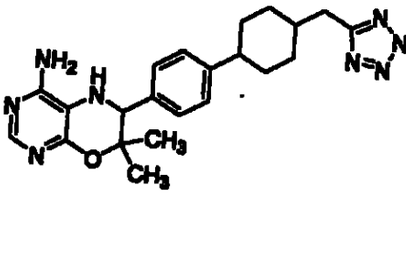


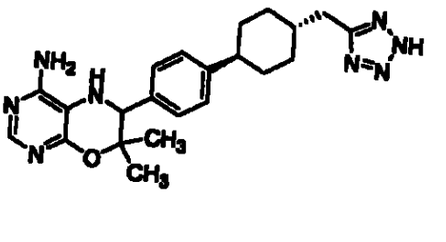


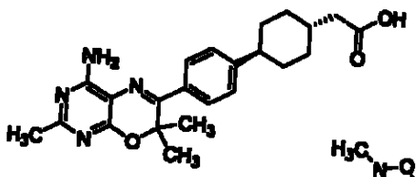


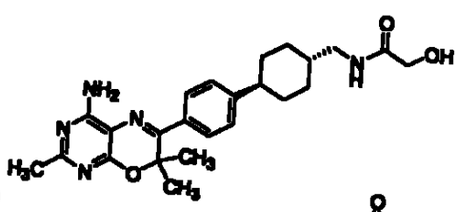


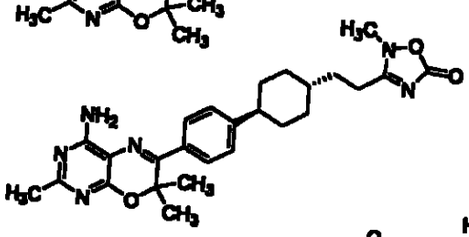


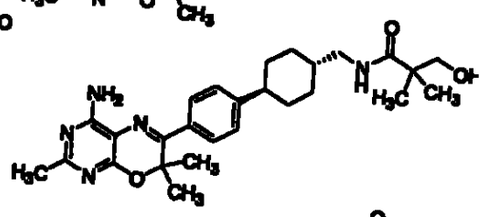


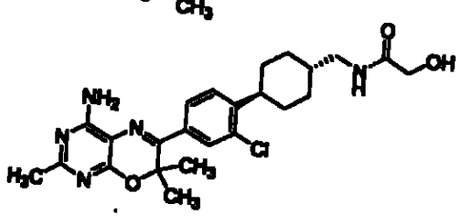


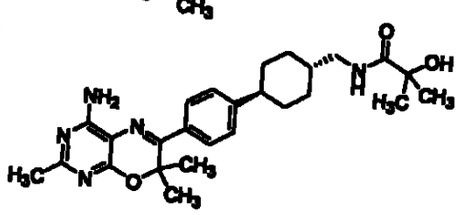


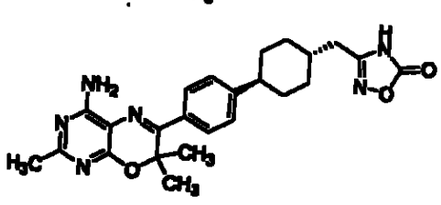


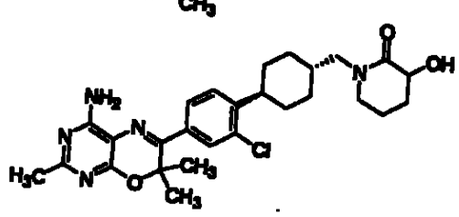


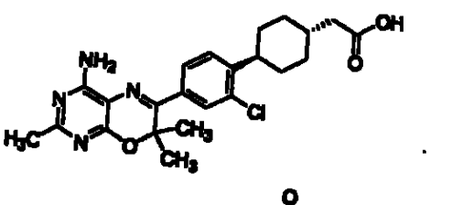


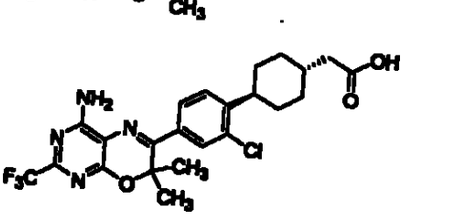


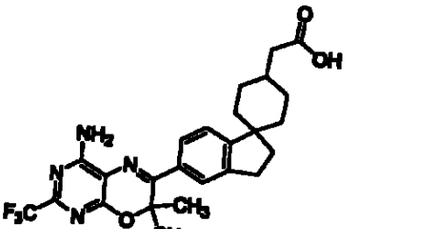


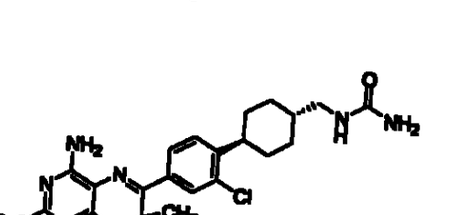


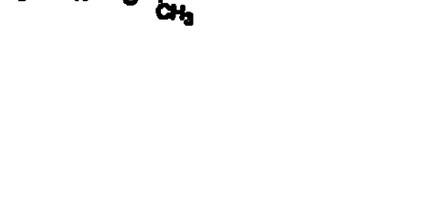


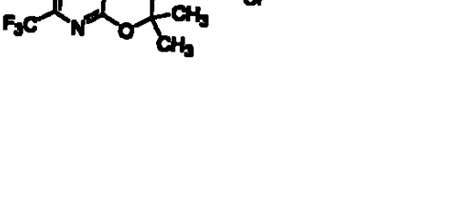


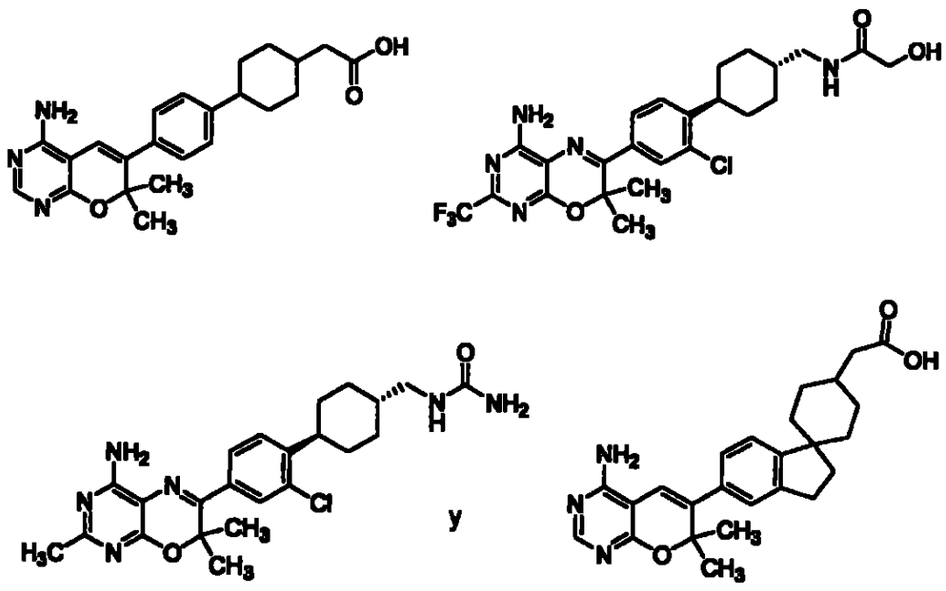










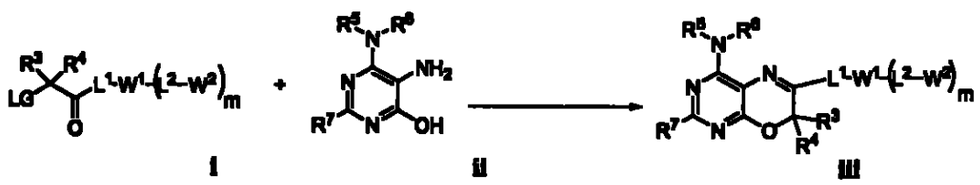


y

Preparación de Compuestos

Pueden prepararse los compuestos de la presente invención comenzando con materiales iniciales disponibles comercialmente y usando las técnicas sintéticas generales conocidas por los expertos en la materia. Posteriormente se presentan esquemas de reacción adecuados para preparar dichos compuestos. Se encuentra ejemplificación adicional en los Ejemplos específicos proporcionados.

Esquema de Reacción 1

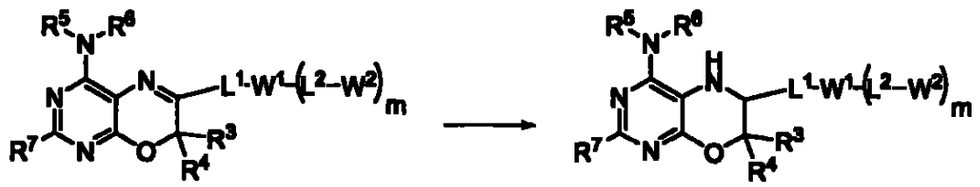


i ii iii

Como se muestra en el Esquema de Reacción 1, compuestos de la presente invención en donde X es N e Y es

N y Z es O, pueden prepararse a partir de una pirimidina (ii) substituida adecuadamente y una cetona (i) substituida en donde LG indica un grupo desplazable tal como un átomo de halógeno, toluensulfonato, metansulfonato o trifluorometansulfonato. La condensación de i e ii en un solvente o mezcla de solventes orgánicos (incluyendo mezclas acuosas) en la presencia o ausencia de un ácido (por ejemplo, HCl) o base (por ejemplo, $NaHCO_3$) proporciona, después de elaborar, un compuesto de Fórmula iii. La reducción de iii con un agente reductor tal como, por ejemplo, borohidruro de sodio, borohidruro de litio o triacetoxiborohidruro de sodio, proporciona aún otros compuestos de la presente invención, ilustrados en el Esquema de Reacción 2.

Esquema de Reacción 2



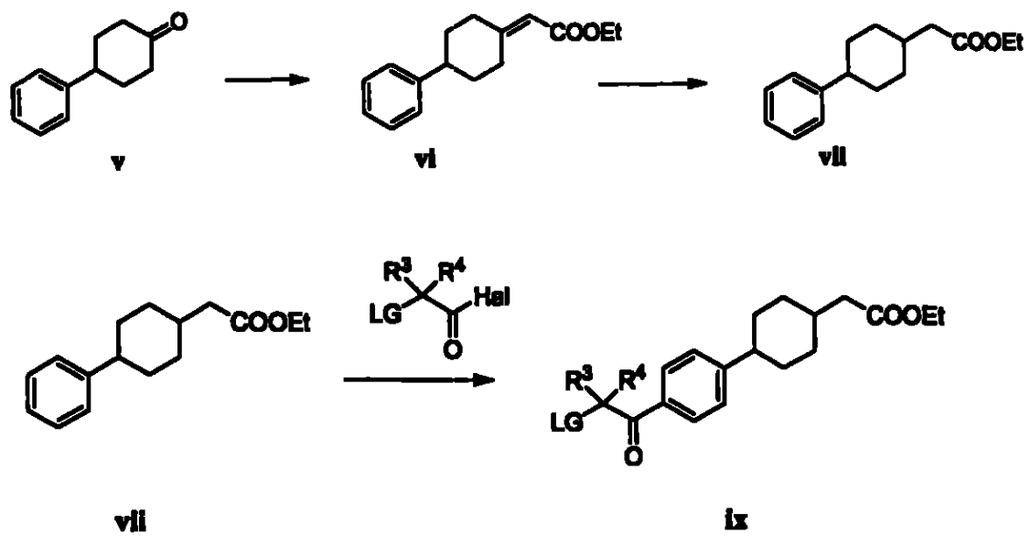
iii iv

Los Esquemas de Reacción 3a-3i ilustran numerosos métodos para la preparación de compuestos intermediarios de Estructura General i. En el Esquema de Reacción 3a, un derivado de benceno, tal como 4-fenil-ciclohexanona (v), es funcionalizado para introducir un substituyente deseado

sobre el anillo ciclohexano. En el ejemplo mostrado, se usó una reacción de Horner-Emmons o similar a Witting para introducir un grupo éster insaturado en α, β, produciendo vi (por ejemplo, la reacción con un fosfonato adecuado en la presencia de una base tal como hidruro de sodio en un solvente tal como DMF o THF). Se usó la hidrogenación catalítica de vi usando, por ejemplo, un catalizador de paladio o de platino en un solvente relativamente polar tal como THF, metanol, o una mezcla acuosa que contiene un alcohol o THF como un co-solvente, por ejemplo, para reducir el doble enlace, produciendo el Compuesto vii. Se usa entonces una reacción de acilación de Friedel-Craft para fijar un grupo haloacetilo sobre el anillo fenilo de vii, formando la acetofenona funcionalizada (ix). Preferiblemente, el grupo desplazable en esta secuencia es Cl o Br. Acidos de Lewis adecuados para la acilación incluyen, por ejemplo, $AlCl_3$, $AlBr_3$, BCl_3, $TiCl_4$, y los similares; solventes adecuados son bien conocidos en el arte, e incluyen CS_2, nitrobenceno, diclorometano, y solventes similares que no son reactivos hacia los reactivos y ácidos de Lewis empleados. Los expertos en la materia apreciarán que se conocen también otros métodos sintéticos para elaborar dichos intermediarios, tales como, por ejemplo, acilación de unas especies aromáticas metaladas, tales como aril-litio aril-Reactivo de

Grignard, con, por ejemplo, un agente acilante tal como un N-metil-N-metoxi amida (comúnmente mencionada como una amida de Weinreb) de un derivado de ácido cloroacético (ver, por ejemplo, Nahm y Weinreb (1981) Tetrahedron Lett. 22: 3815-3818) o un éster de acilo adecuado. Dichos métodos proporcionan accesos a otros isómeros de estos derivados de acetofenona funcionalizados.

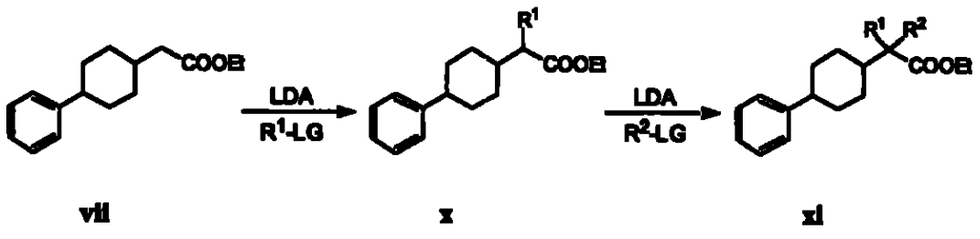
Esquema de Reacción 3a



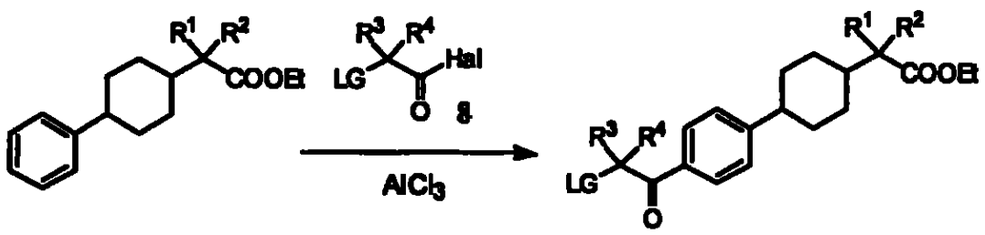
De manera alternativa, vii puede ser alquilado por tratamiento con una base tal como litio diisopropilamida o litio hexametildisilazida en un solvente adecuado tal como THF, seguido por la reacción con un agente alquilante, tal como un haluro de alquilo, metansulfonato de alquilo, trifluorometansulfonato de alquilo o toluensulfonato de alquilo, para dar el intermediario x (Esquema de Reacción

3b). Si se desea, la secuencia puede ser repetida para dar los intermediarios de la Fórmula xi. La acilación de xi puede lograrse como se describió anteriormente para dar xii.

Esquema de Reacción 3b



vii x xi

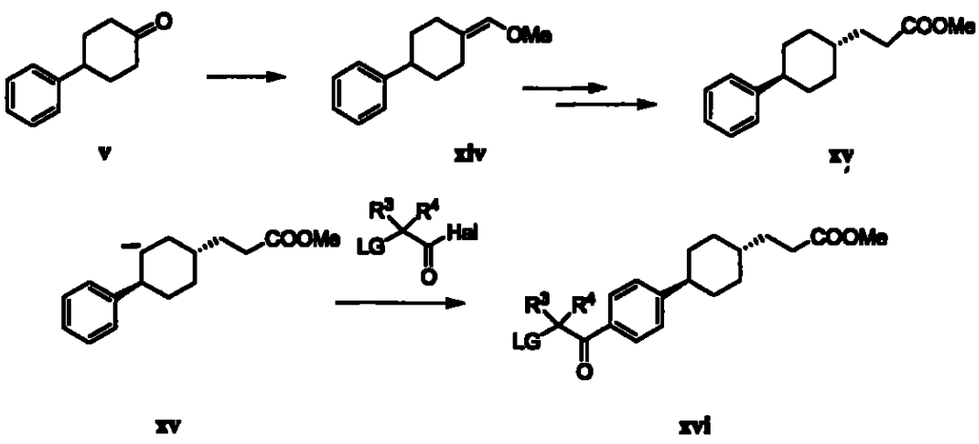


xi xii

Pueden usarse procedimientos similares para producir otros derivados de acetofenonas funcionalizados (ver el Esquema de Reacción 3c). Por ejemplo, 4-fenilciclohexanona (v) puede ser convertida en un aldehido en dos etapas, usando una reacción de Witting con metoximetiltrifenilfosforano en un solvente adecuado tal como THF, DME o dioxano para producir xiv, por ejemplo, seguido por hidrólisis ligeramente ácida. Este aldehido

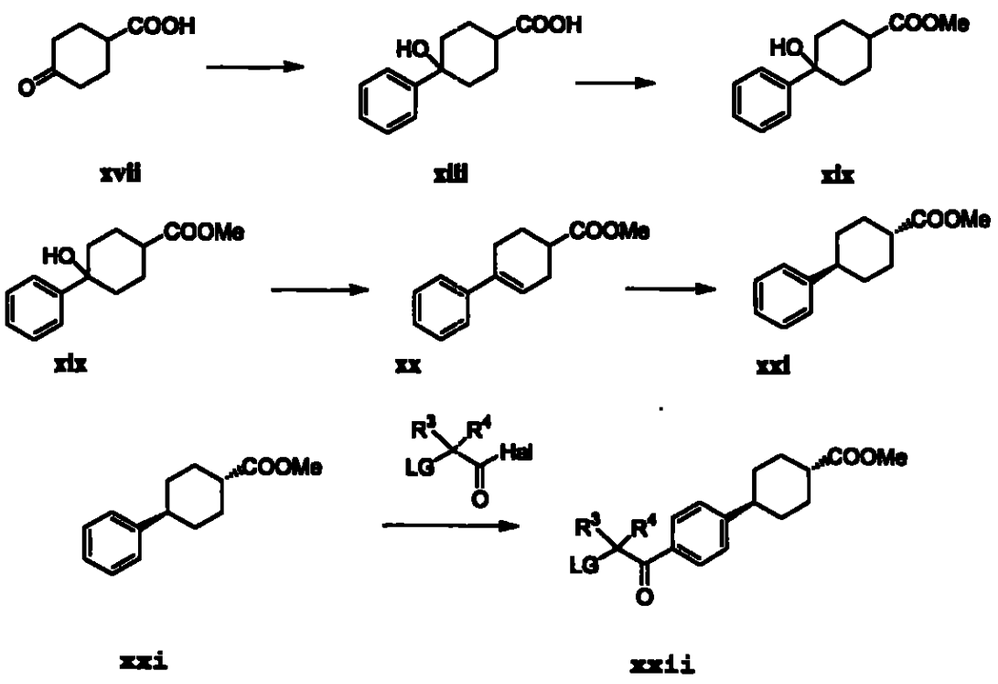
puede ser homologado en un éster insaturado en α,β por medio de una reacción de Witting con (carbometoxi)metilentrifenilfosforano en un solvente adecuado. Si se desea, el doble enlace puede ser reducido vía hidrogenación catalítica usando paladio sobre carbón, por ejemplo, para producir xv. Los solventes adecuados para dichas reacciones de hidrogenación incluyen etanol o acetato de etilo. La acilación de xv para producir un derivado de acetofenona funcionalizado (xvi) puede lograrse como se describe anteriormente por acilación de vii.

Esquema de Reacción 3c



El Esquema de Reacción 3d ilustra la síntesis de otros derivados de acetofenona funcionalizados de Fórmula General i, adecuados para sintetizar compuestos de la presente invención.

Esquema de Reacción 3d



En el Esquema de Reacción 3d, se introduce un grupo fenilo usando, por ejemplo, el ractivo de Grignard-fenilo o fenil-litio para proporcionar xiii. El grupo funcional ácido carboxílico puede ser esterificado bajo condiciones estándares para producir xix, y la deshidratación puede lograrse usando un catalizador ácido tal como ácido acético, ácido clorhídrico o ácido trifluoroacético en un solvente adecuado tal como cloroformo o tolueno para producir xx. La reducción del doble enlace del cilohexeno puede efectuarse bajo condiciones de hidrogenación catalítica usando paladio, típicamente, como el catalizador, para proporcionar xxi. Esta reducción produce una mezcla de isómeros (se produjeron ambos ciclohexanos

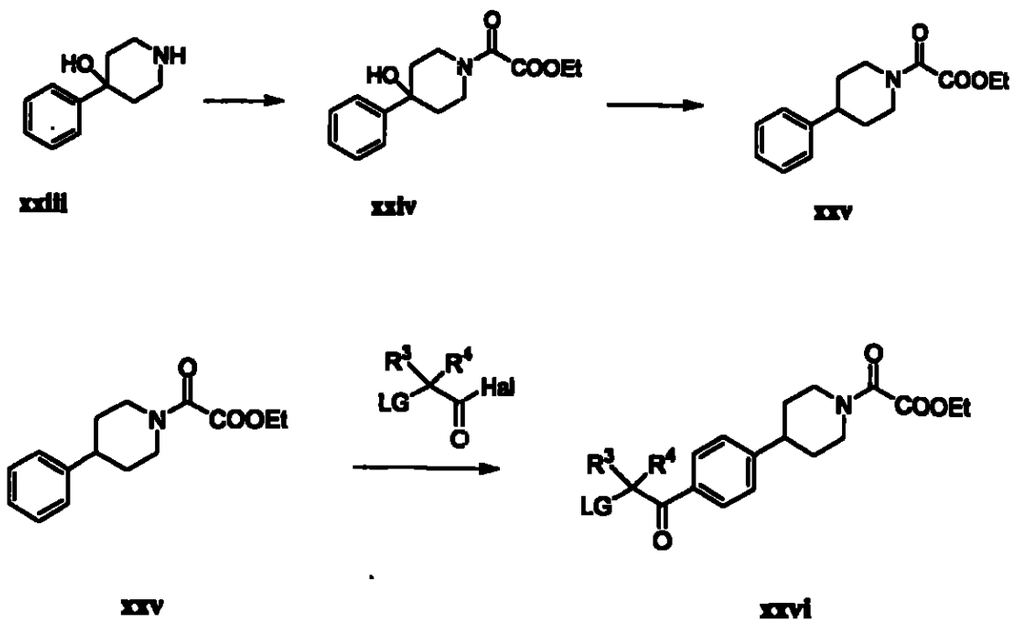
disubstituidos *cis* y *trans*); si se desea, estos pueden ser separados o equilibrados usando una base tal como alcóxido o DBU en metanol o tolueno para producir primeramente el isómero disubstituido trans más estable termodinámicamente. La acilación de xxi para producir la acetofenona funcionalizada xxii se efectúa como se describió anteriormente.

Los compuestos de la presente invención que contienen un anillo heterocíclico para W^2 pueden ser sintetizados por una secuencia similar, a condición de que el anillo heterocíclico sea estable en las condiciones de la reacción de acilación. Por ejemplo, un compuesto donde W^2 es una piperidina acilada puede ser sintetizada de esta manera, usando un derivado de acetofenona funcionalizado tal como el producido por la secuencia mostrada en el Esquema de Reacción 3e. En esta secuencia, 4-hidroxi-4-fenipiperidina (xxiii) es alquilada, sulfonilada o acilada sobre nitrógeno usando reactivos y condiciones conocidas por los expertos en la materia (por ejemplo, acilación con oxalato de dietilo o cloruro de etil oxalilo en la presencia de una base ligera tal como trietilamina o piridina) para producir xxiv. El compuesto de N-funcionalizado (por ejemplo, N-acilado) es luego deshidratado y reducido catalíticamente como se describe anteriormente en el Esquema de Reacción 3d para producir

un oxalato de 4-fenilpiperidina amida (xxv).

Este compuesto es entonces acilado como se describe anteriormente para producir los derivados de acetofenona funcionalizados correspondientes (xxv).

Esquema de Reacción 3e

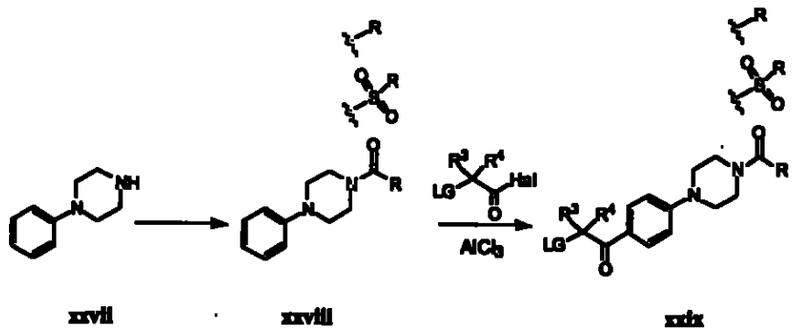


xxiii xxiv xxv

xxv xxvi

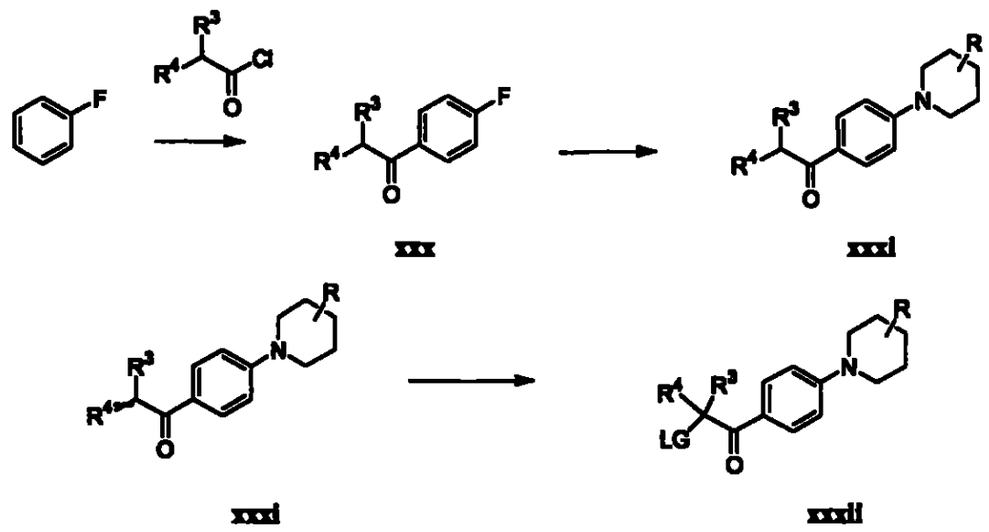
De manera similar, puede ser alquilada la metilpiperazina xxvii, sulfonilada, o acilada sobre nitrógeno para dar el compuesto N-funcionalizado xxviii, el cual puede a su vez ser acilado como se describió previamente para producir el derivado de acetofenona funcionalizado xxix.

Esquema de Reacción 3f



Otros compuestos de la presente invención que tienen un heterociclo como W^2 pueden ser producidos al fijar el grupo heterocíclico sobre una acetofenona, luego halogenar la acetofenona en el carbono α para producir un compuesto de Fórmula General i, como se muestra en el Esquema de Reacción 3g. En esta secuencia, un compuesto de 4-fluoroacetofenona (xxiv) es sintetizado por acilación de fluorobenceno bajo condiciones de Friedel-Craft como se describió anteriormente. El grupo 4-fluor es entonces sometido a reacciones de desplazamiento nucleofílico; en el esquema de reacción es desplazado por un grupo piperidina substituido por reacción con la piperidina nucleofílica en un solvente aprótico polar tal como DMSO o DMF. La funcionalización del átomo de carbono que posee R^3 y R^4 para producir xxvi puede lograrse usando por ejemplo, bromo (Br_2) o cloro (Cl_2) en un solvente polar tal como DME o acetato de etilo, en la presencia de un catalizador ácido tal como ácido acético o ácido bromhídrico.

Esquema de Reacción 3g

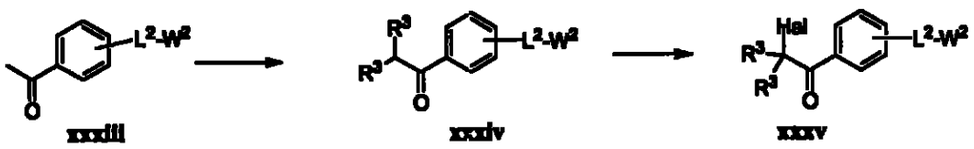


xxx xxxi xxxii xxxiii

Ciertos derivados de acetofenona funcionalizados adecuados para la preparación de compuestos de la presente invención, donde L^1 es un enlace pueden ser preparados a partir de acetofenona substituida, especialmente cuando R^3 y R^4 son grupos idénticos, como se muestra en el Esquema de Reacción 3h. Por ejemplo, una acetofenona substituida con $-L^2-W^2$ (xxxiii) puede ser alquilada con un agente alquilante tal como ioduro de metilo, bromuro de etilo, u otro agente alquilante similar en la presencia de una base tal como litio diisoproilamida, litio hexametildisilazida o hidruro de sodio, y usando un solvente tal como DMF. DME, THF o tolueno. Esto produce una acetofenona donde R3 y R4 son iguales. Esta acetofenona puede entonces ser halogenada como se describió anteriormente en el Esquema

de Reacción 3g para producir una acetofenona funcionalizada de Fórmula General i, la cual se condensará con pirimidinas substituidas como se muestra en el Esquema de Reacción 1 para preparar compuestos de la presente invención.

Esquema de Reacción 3h

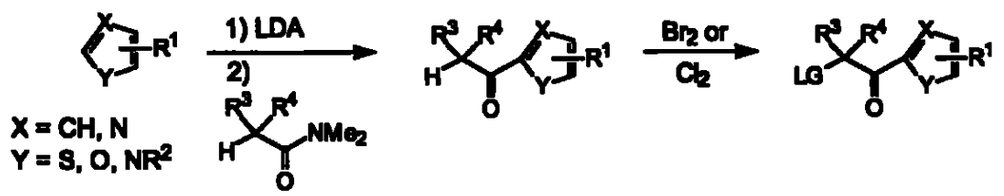


xxxiii xxxiv xxxv

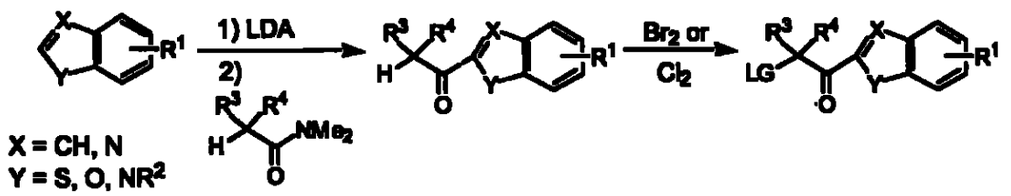
La preparación de los compuestos de la invención que contienen un anillo heterocíclico para W^1 debe de ser sintetizada usando procedimientos similares, como se expone en el Esquema de Reacción 3g. Por ejemplo, un heterociclo substituido o no substituido xxxvi tal como un furano, tiofeno, pirrol, oxazol, tiazol, imidazol o tiadiazol puede ser litiado con, por ejemplo, butil litio o litio diisopropilamida en un solvente adecuado tal como THF, DME o dioxano. Las especies metaladas pueden hacerse reaccionar con, por ejemplo, una amida, tal como una dimetilamida o una N- metil- N- metoxiamida para producir el heterociclo acilado xxxvii, el cual a su vez puede ser halogenado como se describió anteriormente para producir un derivado de acetofenona funcionalizado de Fórmula General xxxviii. En una secuencia similar, un benzofurano

substituido o no substituido, benzotiofeno, benzopirrol, benzoxazol, benzotiazol, bencimidazol o benzotiadiazol (xxxix) pueden ser litiados y acilados para dar xl, el cual a su vez puede ser halogenado como se describió previamente. Un experto en la materia apreciará que pueden usarse también otros heterociclos en estas transformaciones.

Esquema de Reacción 3i



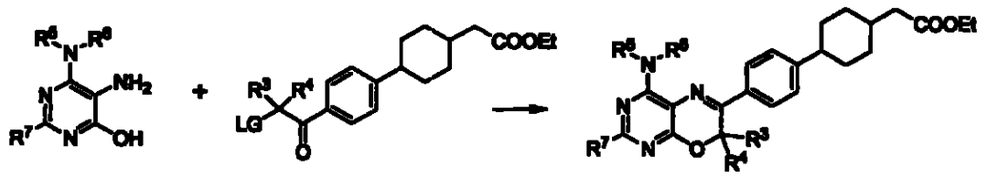
xxxvi xxxvii xxxviii



xxxix xl xli

Como se muestra en el Esquema de Reacción 4, compuestos de Fórmula General iv que tienen un anillo fenilo substituido como W^1 y un anillo ciclohexano substituido como L^2-W^2 (por ejemplo, xlii) pueden preparase a partir de estos derivados de acetofenona similares a ix.

Esquema de Reacción 4

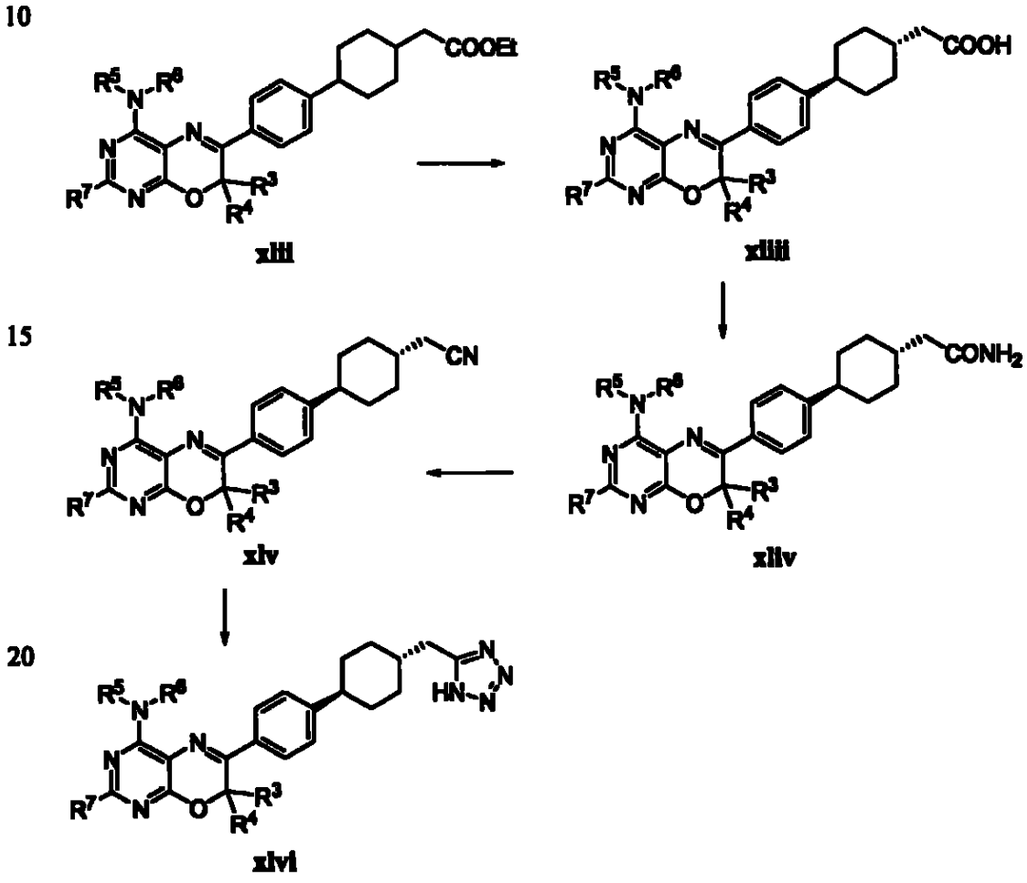


ii ix xliii

Pueden usarse compuestos tales como xlii para elaborar otros compuestos de la presente invención, por ejemplo, por hidrólisis del éster etílico para proporcionar un compuesto de ácido carboxílico (Esquema de Reacción 5). La hidrólisis del éster puede lograrse en la mayoría de los solventes que disolverán xlii y son al menos parcialmente miscibles con agua, al tratar una solución de xlii con la base acuosa tal como hidróxido de sodio o hidróxido de potasio, por ejemplo. El ácido carboxílico puede a su vez, ser convertido en otros grupos como una amida por medio de métodos bien conocidos por los expertos en la materia. Por ejemplo, el ácido carboxílico puede ser activado por condensación por una variedad de reactivos de acoplamiento, incluyendo hidroxibenzotriazol (HOBt) y N-Hidroxisuccinimida (HOSu), por ejemplo, usando diciclohexilcarbodiimida (DCC) o un reactivo de carbodiimida similar o una amplia variedad de reactivos tales como los desarrollados para la formación de enlaces peptídicos. Las condiciones para dichas reacciones son

bien conocidas por los expertos en la materia. El intermediario activado, un éster de HOBt o HOSu, por ejemplo, puede entonces ser condensado con una variedad de nucleófilos tales como, por ejemplo, aminas, alcoholes y tioles. El Esquema de Reacción 5 muestra la conversión de un compuesto de Fórmula xlii en una amida (xiv) por esta secuencia, usando amoníaco como el nucleófilo.

Esquema de Reacción 5

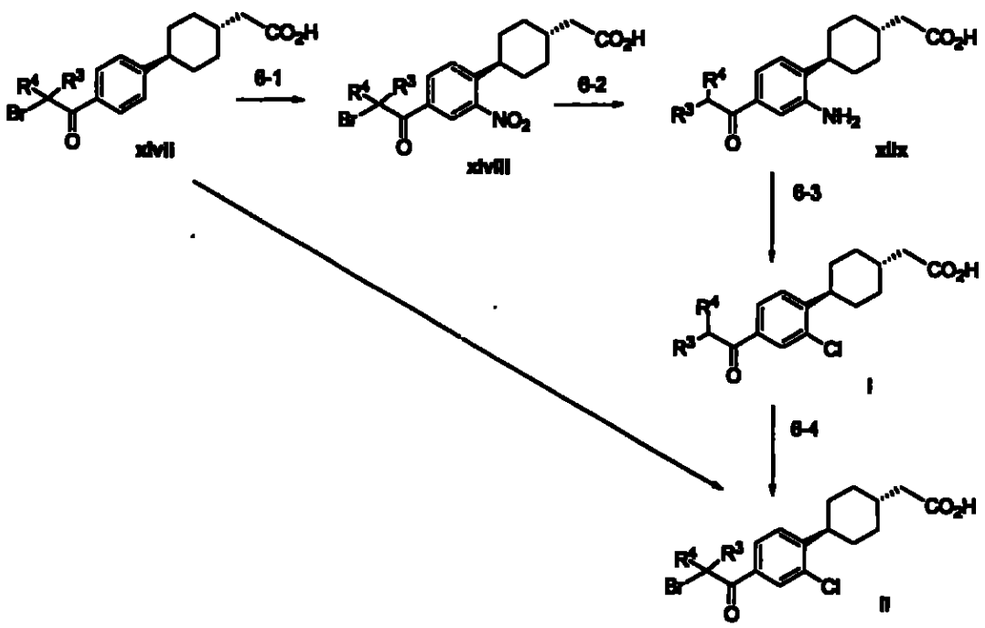


La deshidratación de la amida xlv a un nitrilo (xiv) puede lograrse por medio de una variedad de métodos. Ver el Esquema de Reacción 5 anterior. El pentóxido de fósforo es el más común reactivo deshidratante para esta reacción, pero muchos otros son conocidos por los expertos en la materia. El nitrilo puede ser, a su vez, convertido en otros grupos tales como tetrazol (xlvi) por métodos bien conocidos por los expertos en la materia. Por ejemplo, haciendo reaccionar el nitrilo con una azida, tal como azida de sodio, azida de litio o ácido hidrazoico en un solvente tal como DMF o agua, se logrará esta transformación.

Los Esquemas de Reacción 6a y 6b ilustran un procedimiento para la preparación de compuestos de Fórmula I en la cual W1 es una porción fenileno que tiene unos substituyentes adicionales diferentes del componente L2-W2. Como se ve en el Esquema de Reacción 6a, bromoacetofenonas (xlvii) intermediarias pueden ser nitradas bajo condiciones estándares (ácido nítrico, ácido sulfúrico en solventes tales como cloroformo, cloruro de metileno, ácido acético, o puro) para proporcionar xlviii. La reducción del grupo nitro es acompañada por desbromación para proporcionar xlix usando hidrogenación catalítica o $SnCl_2$ (generalmente en solventes alcohólicos). El reemplazo del cloruro del grupo amino se

logra usando cloruro de cobre en la presencia de un nitrito adecuado (por ejemplo, nitrito de t-butilo, nitrito de sodio) y solvente, para proporcionar intermediarios tales como I. El bromo puede ser reintroducido, proporcionando li usando técnicas de bromación estándares (por ejemplo, HBr/HOAc, Br_2/N-bromosuccinimida o $CuBr_2$). Alternativamente, xlvii puede ser clorado directamente para proporcionar li usando reactivos estándares (por ejemplo, cloruro de sulfurilo, Cl_2 o N-clorosuccinimida) y las condiciones conocidas por los expertos en la materia.

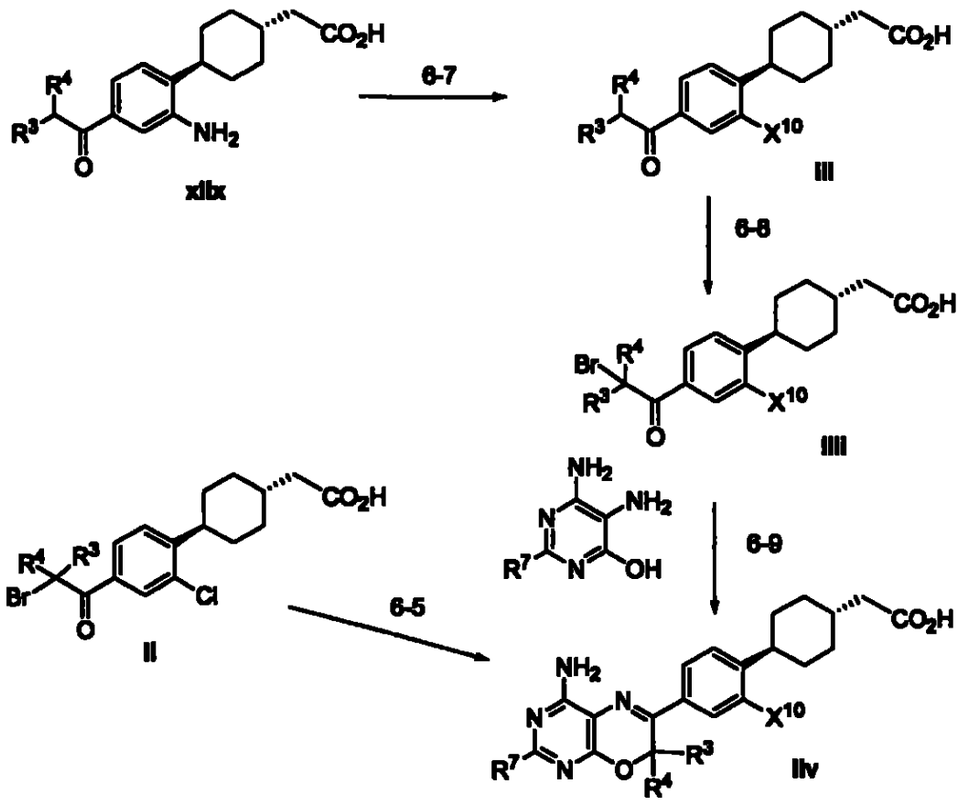
Esquema de Reacción 6a



El Esquema de Reacción 6b ilustra la elaboración de intermediarios tales como xlix para otros compuestos

substituidos. Por ejemplo, compuestos de Fórmula lii (en donde X^{10} es F) pueden ser producidos a partir de xlix usando reactivos fluorados tales como tetrafluoroborato de nitrosonio, DAST, HF o CsF (generalmente en solventes tales como tolueno, benceno, cloruro de metileno o diclorometano). La bromación subsecuente de lii para producir liii puede lograrse de conformidad con métodos conocidos. La conversión de li o de liii o de ambos a compuestos objetivo de la Fórmula liv se logra vía condensación con una pirimidina substituida adecuadamente (ver el Ejemplo 1).

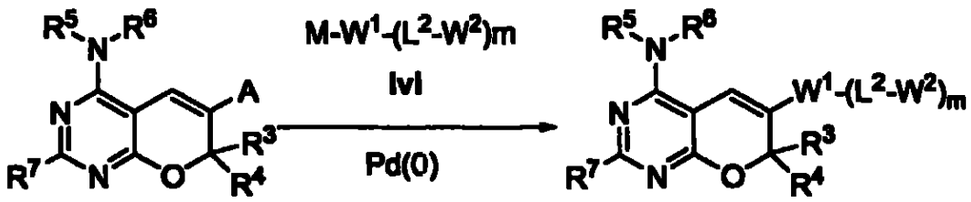
Esquema de Reacción 6b



Como se muestra en el Esquema de Reacción 7, los compuestos de la presente invención en donde X es N, Y es CH, Z es O y W^1 es un arilc o heteroarilo substituido o no substituido pueden prepararse a partir de pirimidina lv substituida adecuadamente (donde A es un halógeno, por ejemplo, Br, I o un triflato u otro substituyente adecuado conocido en el arte) y unas especies lvi arilo o heteroarilo substituidos c no substituidos (donde M es $B(OR^2)$, $Sn(R^3)$ u otros metales adecuados conocidos por los expertos en la materia) por ejemplo, por medio de una

reacción cruzada catalizada con paladio. Los expertos en la materia también apreciarán que A y M pueden ser intercambiados.

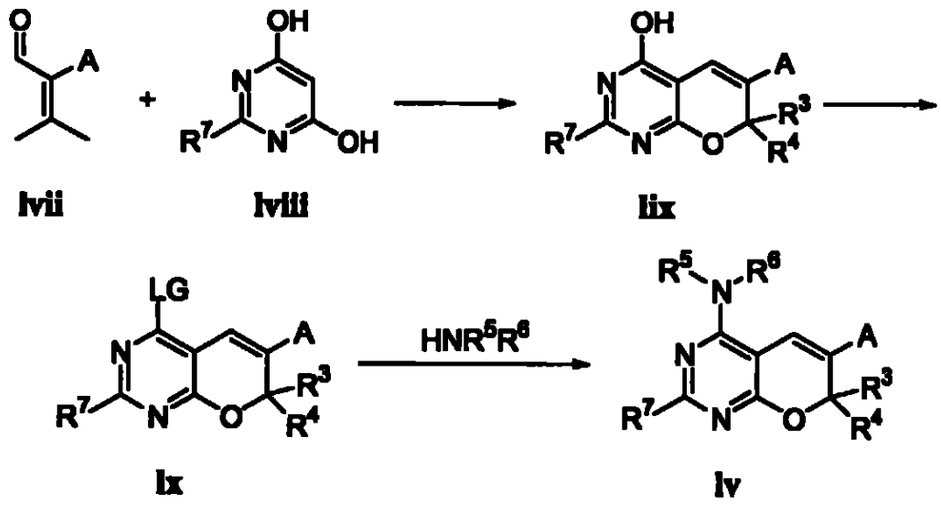
Esquema de Reacción 7



lv

El Esquema de Reacción 8, ilustra un método para la preparación del intermediario de Estructura General lv. La condensación de pirimidina lviii con lvii en un solvente adecuado tal como ácido acético da lix. La conversión de la porción hidroxi a un grupo desplazable, por ejemplo, un cloruro o bromuro con, por ejemplo, oxicloruro de fósforo u oxibromuro de fósforo respectivamente, es seguido por el desplazamiento del grupo desplazable con una amina substituida adecuadamente para dar lv.

Esquema de Reacción 8



Composiciones

En otro aspecto, la presente invención proporciona composiciones farmacéuticas para modular la actividad de DGAT en humanos y en animales que contienen típicamente un compuesto de Fórmula I y un portador o diluyente aceptable farmacéuticamente.

Las composiciones farmacéuticas para la administración de los compuestos de esta invención pueden ser presentadas convenientemente en forma de dosificación unitaria y pueden ser preparadas por medio de cualquiera de los métodos bien conocidos en el arte de farmacia. Todos los métodos incluyen la etapa de poner el ingrediente activo en asociación con el portador, lo cual constituye uno o más ingredientes accesorios. En general, las composiciones farmacéuticas son preparadas poniendo el

ingrediente activo en asociación íntima y uniforme con un portador líquido o un portador sólido finamente dividido o ambos, y luego, si es necesario, conformar el producto en la formulación deseada. En la composición farmacéutica el compuesto activo objetivo es incluido en una cantidad suficiente para producir el efecto deseado en el proceso o condición de enfermedades.

Las composiciones farmacéuticas que contienen el ingrediente activo pueden estar en la forma adecuada para uso oral, por ejemplo, como tabletas, pastillas, lozanges, suspensiones acuosas u oleosas, polvos o gránulos dispersables, emulsiones, cápsulas duras o blandas, o jarabes, o elíxires. Las composiciones previstas para uso oral pueden ser preparadas de conformidad con cualquier método conocido en el arte para la fabricación de composiciones farmacéuticas. Dichas composiciones pueden contener uno o más agentes seleccionados a partir de agentes edulcorantes, agentes aromatizantes, agentes colorantes y agentes conservadores a fin de proporcionar preparaciones paladeables y elegantes farmacéuticamente. Las tabletas contienen el ingrediente activo en mezcla con otros excipientes aceptables farmacéuticamente no tóxicos que sean adecuados para la fabricación de tabletas. Estos excipientes pueden ser por ejemplo, diluyentes inertes, tales como carbonato de calcio, carbonato de sodio,

lactosa, fosfato de calcio o fosfato de sodio, agentes granuladores o desintegrantes, por ejemplo, almidón de maíz, o ácido algínico; agentes aglutinantes, por ejemplo, almidón, gelatina o acacia, y agentes lubricantes, por ejemplo, estearato de magnesio, ácido esteárico o talco. Las tabletas pueden ser sin recubrir o pueden ser recubiertas por medio de técnicas conocidas para retardar la desintegración y la absorción en el tracto gastrointestinal y pueden proporcionar así una acción controlada durante un período prolongado. Por ejemplo, puede emplearse un material de retardo del tiempo tal como monoestearato de glicerilo o diestearato de glicerilo. Pueden también ser recubiertas por medio de las técnicas descritas en las Patentes U.S. Nos. 4,256,108; 4,166,452; y 4,265,874 para formar tabletas terapéuticas osmóticas para liberación controlada.

Las formulaciones para uso oral pueden presentarse como cápsulas de gelatina dura en donde el ingrediente activo es mezclado con un diluyente sólido inerte, por ejemplo, carbonato de calcio, fosfato de calcio o caolín, o como cápsulas de gelatina blanda en donde el ingrediente activo es mezclado con agua o con un medio oleoso, por ejemplo aceite de cacahuate, parafina líquida, o aceite de olivo.

Las suspensiones acuosas contienen los materiales

activos en mezcla con excipientes adecuados para la fabricación de suspensiones acuosas. Dichos excipientes son agentes formadores de suspensiones, por ejemplo carboximetilcelulosa sódica, metilcelulosa, hidroxipropilmetil celulosa, alginato de sodio, polivinil pirrolidona, goma de tragacanto y goma de acacia; los agentes dispersantes o humectantes pueden ser fosfatidas como se encuentran naturalmente, por ejemplo lecitina, o productos de condensación de un óxido de alquileno con ácidos grasos, por ejemplo estearato de polioxietileno, o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetilenoxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol tal como monooleato de polioxietilen sorbitol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y de anhídridos de hexitol, por ejemplo monooleato de polietilen sorbitan. Las suspensiones acuosas pueden contener uno o más conservadores, por ejemplo etilo, o n-propilo, p-hidroxibenzoato, uno o más agentes colorantes, uno o más agentes aromatizantes, y uno o más agentes edulcorantes, tales como sacarosa o sacarina.

Las suspensiones oleosas pueden ser formuladas suspendiendo el ingrediente activo en un aceite vegetal,

por ejemplo aceite de girasol, aceite de olivo, aceite de sésamo o aceite de coco, o en un aceite mineral tal como parafina líquida. Las suspensiones oleosas pueden contener un agente espesante, por ejemplo cera de abeja, parafina dura o alcohol cetílico. Los agentes edulcorantes tales como los expuestos anteriormente, y agentes aromatizantes pueden ser añadidos para proporcionar una preparación oral paladeable. Estas composiciones pueden ser conservadas por la adición de un anti-oxidantes tales como ácido ascórbico.

Los polvos y gránulos dispersables adecuados para la preparación de una suspensión acuosa por medio de la adición de agua proporciona el ingrediente activo en mezcla con un agente dispersante o humectante y agentes de formadores de suspensiones son ejemplificados por los ya mencionados anteriormente. Pueden también estar presentes excipientes adicionales, por ejemplo agentes edulcorantes, aromatizantes y colorantes.

Las composiciones farmacéuticas de la invención pueden también estar en la forma de emulsiones de aceite en agua. La fase oleosa puede ser un aceite vegetal, por ejemplo aceite de olivo o aceite de girasol, o un aceite mineral, por ejemplo parafina líquida o mezclas de las mismas. Los agentes emulsificantes adecuados pueden ser gomas como se encuentran de manera natural, por ejemplo,

goma de acacia o goma de tragacanto, fosfatidas como se encuentran naturalmente, por ejemplo soya, lecitina, y ésteres o ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo monooleato de sorbitan, y productos de condensación de los ésteres parciales con óxido de etileno, por ejemplo monooleato de polioxietilen sorbitan. Las emulsiones pueden contener también agentes edulcorantes y agentes aromatizantes.

Los jarabes y elíxires pueden ser formulados con agentes edulcorantes, por ejemplo glicerol, propilen glicol, sorbitol o sacarosa. Dichas formulaciones pueden también contener un demulcente, un conservador y aromatizante y agentes colorantes.

Las composiciones farmacéuticas pueden estar en la forma de una suspensión oleaginosa o acuosa inyectable estéril. Esta suspensión puede ser formulada de conformidad con el arte conocido usando los agentes humectantes o dispersantes adecuados que han sido mencionados anteriormente. La preparación inyectable estéril puede también ser una solución o suspensión inyectable estéril en un solvente o diluyente aceptable parenteralmente no tóxico, por ejemplo como una solución en 1,3-butano diol. Entre los vehículos y solventes aceptables que pueden ser empleados, están el agua, la solución de Ringer y solución isotónica de cloruro de

sodio. Además, los aceites fijos son empleados convencionalmente como un solvente o medio de suspensión. Para este propósito puede emplearse cualquier aceite fijo blando incluyendo mono- o diglicéridos sintéticos. Además, ácidos grasos tales como ácido oleico tienen uso en la preparación de inyectables.

Los compuestos de la presente invención pueden también ser administrados en la forma de supositorios para administración rectal del fármaco. Estas composiciones pueden ser preparadas al mezclar el fármaco con un excipiente no irritante adecuado, que sea sólido a temperaturas ordinarias pero líquidos a la temperatura rectal y por consiguiente se fundirán en el recto para liberar el fármaco. Dichos materiales son manteca de cacao y polietilen glicoles.

Para uso tópico, se emplean parches, cremas, ungüentos, jaleas, soluciones o suspensiones, etc., que contienen los compuestos de la presente invención. Como se usa en la presente, la aplicación tópica quiere decir que incluye el uso de lavados y gárgaras bucales.

La composición farmacéutica y los métodos de la presente invención pueden comprender adicionalmente otros compuestos activos terapéuticamente como se hace notar en la presente son aplicados usualmente en el tratamiento de las condiciones patológicas anteriormente mencionadas.

Métodos de Uso

En aún otro aspecto, la presente invención proporciona métodos de usar un compuesto o composición de la invención para tratar o prevenir una enfermedad o condición asociada con DGAT. Las enfermedades y condiciones asociadas con el metabolismo lipídico y la proliferación celular, y complicaciones de las mismas, pueden ser tratadas con los compuestos y composiciones objetivo. En un grupo de modalidades, las enfermedades y condiciones, que incluyen enfermedades crónicas, de humanos o de otras especies que pueden ser tratadas con inhibidores de la función de DGAT incluyen, pero no se limitan a, trastornos metabólicos, tales como obesidad, diabetes, anorexia nerviosa, bulimia, caquexia, síndrome X, resistencia a la insulina, hipoglicemia, hiperglicemia, hiperuricemia, hiperinsulinemia, hipercolesterolemia, hiperlipidemia, dislipidemia, dislipidemia mezclada, hipertrigliceridemia y enfermedades hepáticas grasas no alcohólicas; enfermedades cardiovasculares, tales como arterioesclerosis, falla cardíaca aguda, falla cardíaca congestiva, enfermedad de la arteria coronaria, cardiomiopatía, infarto al miocardio, angina pectoris, hipertensión, hipotensión, apoplejía, isquemia, daños por reperfusión isquémica, aneurisma, restenosis y estenosis vascular; enfermedades neoplásticas, tales como tumores

sólidos, cáncer de la piel, melanoma, linfoma y cánceres endoteliales, por ejemplo, cáncer de seno, cáncer pulmonar, cáncer colonrectal, cáncer estomacal, otros cánceres del tracto gastrointestinal (por ejemplo, cáncer esofágico y cáncer pancreático), cáncer de la próstata, cáncer de riñón, cáncer de hígado, cáncer de vejiga, cáncer cervical, cáncer uterino, cáncer testicular, y cáncer ovárico; y otras enfermedades y condiciones que son sensibles o responsables de la modulación de la función de DGAT.

Los métodos de la presente invención típicamente involucran administrar a un sujeto en necesidad de tratamiento terapéutico, una cantidad efectiva de un compuesto de Fórmula (I). La dosis, frecuencia y distribución de la administración dependerá en gran parte del agente terapéutico seleccionado, la naturaleza de la condición que es tratada, la condición del sujeto incluyendo edad, peso y presencia de otras condiciones o trastornos, la formulación que es administrada y la discreción del médico que atiende. Preferiblemente, las composiciones y compuestos de la invención y las sales de los mismos aceptables farmacéuticamente son administrados vía las rutas oral, parenteral o tópica. Generalmente, los compuestos son administrados en dosificaciones que varían de aproximadamente 2 mg a aproximadamente 2,000 mg por

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día, aunque necesariamente habrán variaciones que dependen, como se hizo notar anteriormente, de la enfermedad objetivo, del paciente, y de la ruta de administración. Se administran oralmente dosificaciones preferidas en el intervalo de aproximadamente 0.05 mg/kg a aproximadamente 20 mg/kg, más preferiblemente en el intervalo de aproximadamente 0.05 mg/kg a aproximadamente 2 mg/kg, más preferiblemente en el intervalo de aproximadamente 0.05 mg/kg a aproximadamente 0.2 mg por kg de peso corporal por día. La dosificación empleada para la administración tópica, por supuesto, depende del tamaño del área a ser tratada.

Terapia en combinación con agentes activos adicionales

La presente invención proporciona adicionalmente métodos de usar un compuesto o composición de la invención en combinación con uno o más agentes activos adicionales, dependiendo de la terapia objetivo deseada (ver, por ejemplo, Turner, N. y colaboradores Prog. Drug. Res. (1998) 51:33-94; Haffner, S. Diabetes Care (1998) 21: 160-178; y DeFronzo, R., y colaboradores (eds.), Diabetes Reviews (1997) Vol. 5 No. 4). Numerosos estudios han investigado los beneficios de las terapias en combinación con agentes orales (ver, por ejemplo, Mahler, T. J. Clin. Endocrinol. Metab. (1999) 84: 1165-71; United Kingdom

(42)

Prospective Diabetes Study Group: UKPDS 28, Diabetes Care (1998) 21: 87-92; Bardin, C. W., (ed.), CURRENT THERAPY IN ENDOCRINOLOGY AND METABOLISM, 5TH. Edtion (Mosby - Year Book, Inc., St. Louis, MO 1997); Chiasson, J. y colaboradores, Ann. Intern. Med. (1994) 121: 928-935; Coniff, R. y colaboradores, Clin. Ther. (1997) 19: 16-26; Coniff, R. y colaboradores, Am. J. Med. (1995) 98: 443-451; e Iwamoto, Y. y colaboradores, Diabet. Med. (1996) 13 365-370; Kwiterovich, P. Am. J. Cardiol (1998) 82 (12A): 3U-17U).

En particular los estudios proporcionados anteriormente indican que la modulación de la diabetes y de la hiperlipidemia puede ser mejorada adicionalmente en muchos casos por la adición de un segundo agente para el régimen terapéutico. La terapia en combinación incluye la administración de una formulación de dosificación farmacéutica única que contiene un compuesto que tiene la estructura general de Fórmula I y uno o más agentes activos adicionales, así como también la administración de un compuesto de Fórmula I y cada agente activo en su propia formulación farmacéutica separada. Por ejemplo, puede administrarse al sujeto humano, un compuesto de Fórmula I y un inhibidor de HMG-CoA reductasa junto con una composición de dosificación oral única, tal como una tableta o cápsula, o cada agente puede ser administrado en

formulaciones de dosificación oral separadas. Cuando se usan formulaciones de dosificación separada, un compuesto de fórmula I y uno o más agentes activos adicionales pueden ser administrados esencialmente al mismos tiempo (es decir, concurrentemente), o a tiempos escalonados separadamente (es decir, secuencialmente). Se comprende que la terapia en combinación incluye todos estos regímenes.

Un ejemplo de terapia en combinación que modula (previene el principio de los síntomas o complicaciones asociadas con) arterioesclerosis involucra administrar un compuesto de fórmula I en combinación con uno o más de los siguientes agentes activos: un agente antihiperlipidémico; un agente que aumenta el HDL plasmático; un agente anti-hipercolesterolémico, tal como un inhibidor de la biosíntesis del colesterol, por ejemplo, un inhibidor de hidroximetilglutaril (HMG) CoA reductasa (también mencionado como estatinas, tales como lovastatina, simvastatina, pravastatina, fluvastatina, y atorvastatina), un inhibidor de HMG-CoA sintasa, un inhibidor de escualeno epoxidasa, o un inhibidor de escualeno sintetasa (también conocido como inhibidor de escualeno sintasa); un inhibidor de acil-coenzima A colesterol aciltransferasa (ACAT), tal como melinamida; probucol; ácido nicotínico y las sales de los mismos y

niacinamida; un inhibidor de la absorción de colesterol, tal como β-sitosterol; una resina de intercambio aniónico secuestrante de ácidos biliares, tal como colestiramina, colestipol o derivados de dialquilaminoalquilo de un dextrano reticulado; un inductor del receptor de LDL (lipoproteína de baja densidad); fibratos, tales como clofibrato, bezafibrato, fenofibrato, y gemfibrizol; vitamina B6 (también conocida como piridoxina) y sales se los mismos aceptables farmacéuticamente, tales como la sal HCl; vitamina B12 (también conocida como cianocobalamina); vitamina B3 (también conocida como ácido nicotínico y niacinamida, supra); vitaminas anti-oxidantes, tales como vitamina C y E y beta carotenos; un bloqueador beta; un antagonista de angiotensina II; un inhibidor de la enzima convertidora de angiotensina; y un inhibidor de la aglutinación plaquetaria, tal como antagonistas de receptor de fibrinógeno (es decir, antagonistas del receptor de glicoproteína IIb/ fibrinógeno IIIa) y aspirina. Como se hizo notar anteriormente, los compuestos de Fórmula I pueden ser administrados en combinación con más de un agente activo adicional, por ejemplo, una combinación de un compuesto de Fórmula I con un inhibidor de HMG-CoA reductasa (por ejemplo, lovastatina, simvastatina y pravastatina) y aspirina, o un compuesto de Fórmula I con un inhibidor de HMG-CoA reductasa y un

bloqueador β.

Otro ejemplo de terapia en combinación puede verse en el tratamiento de la obesidad o trastornos relacionados con la obesidad, en donde los compuestos de la Fórmula I puede ser usado efectivamente usado en combinación con, por ejemplo, fenilpropanolamina, fentermina, dietilpropion, mazindol; fenfluramina, dexfenfluramina, fentiramina, agentes agonistas del adrenoreceptor β3; sibutramina, inhibidores de la lipasa gastrointestinal (tales como Orlistat), y leptinas. Otros agentes usados al tratar la obesidad o trastornos relacionados con la obesidad pueden ser usados en combinación con compuestos de Fórmula I que incluyen por ejemplo, neuropéptido Y, enterostatina, colecistoquina, bombesina, amilina, receptores de histamina H3, receptores de dopamina D2, hormona estimuladora de melanocito, factor de liberación de corticotrofina, galanina y ácido amino butírico gama (GABA).

Otro ejemplo de terapia en combinación puede verse al modular la diabetes (o tratar la diabetes y sus síntomas, complicaciones, y trastornos relacionados), en donde los compuestos de Fórmula I pueden ser usados efectivamente en combinación con, por ejemplo, sulfonilureas (tales como clorpropamida, tolbutamida, acetohexamida, tolazamida, gliburida, glicazida, glinasa, glimepirida, y glipizida,

biguanidas (tales como metformina), tiazolidindionas (tales como ciglitazona, pioglitazona, troglitazona, y rosiglitazona); deshidroepiandrosterona (también mencionada como DHEA o su sulfato éster conjugado, DHEA-SO_4); antiglucocorticoides; inhibidores de TNF-α; inhibidores de α-glucosidasa (tal como acarbosa, miglitol, y voglibosa), pramlintida /un análogo sintético de la hormona amilina humana), otros secretagogos de insulina (tales como rapaglinida, gliquidona, y nateglimida), insulina, así como también los agentes activos discutidos anteriormente para tratar arterioesclerosis.

Aún otro aspecto de terapia en combinación puede verse al modular hiperlipidemia (tratar hiperlipidemia y sus complicaciones relacionadas), en donde los compuestos de Fórmula I pueden ser usados efectivamente en combinación con, por ejemplo, estatinas (tales como fluvastatina, lovastatina, pravastatina o simvastatina), resinas de enlace de ácidos biliares (tales como colestipol o colestiramina), ácido nicotínico, probucol, betacarotenos, vitamina E, o vitamina C.

De conformidad con la presente invención, una cantidad efectiva terapéuticamente de un compuesto de Fórmula I pueden ser usados para la preparación de una composición farmacéutica útil para tratar diabetes, tratar hiperlipidemia, tratar hiperuricemia, tratar obesidad,

niveles de triglicéricos decrecientes, niveles de colesterol decrecientes, elevación del nivel plasmático de lipoproteínas de alta densidad, y para tratar, prevenir o reducir el riesgo de desarrollar arterioesclerosis.

Un ejemplo adicional de terapia en combinación puede verse al modular condiciones dermatológicas, en donde los compuestos de Fórmula I pueden ser usados efectivamente en combinación con, por ejemplo, tratamientos del acné (por ejemplo isotretinoina, doxiciclina, tetraciclina, salicilato) y tratamientos de dermatitis seborreica (agentes antifúngicos tales como climbazol, ketoconazol). Además, compuestos de Fórmula I pueden ser usados efectivamente para mejorar la liberación transdérmica de fármacos aplicados tópicamente en la forma de un parche, loción, jalea, crema, etc.

Aún otro ejemplo adicional de terapia en combinación puede verse en el tratamiento de enfermedades hepáticas grasas no alcohólica (NAFLD), en donde compuestos de Fórmula I pueden ser usados efectivamente en combinación con agentes hematopoyéticos tales como ácido ursodesoxicólico y betaína.

Adicionalmente, una cantidad efectiva de un compuesto de Fórmula I y una cantidad efectiva terapéuticamente de uno o más agentes activos seleccionados del grupo que consiste de: un agente antihiperlipidémico; un agente

elevador del HDL plasmático, un agente anti-hipercolesterolémico, tal como un inhibidor de la biosíntesis del colesterol, por ejemplo, un inhibidor de HMG-CoA reductasa, un inhibidor de HMG-CoA sintasa, un inhibidor de escualeno sintasa, o un inhibidor de escualeno sintetasa (también conocido como inhibidor de escualeno sintasa); un inhibidor de acil-co-enzima A colesterol aciltransferasa, probucol; ácido nicotínico y sales de los mismos; niacinamida, un inhibidor de la absorción de colesterol; una resina aniónica secuestrante de ácidos biliares; un inductor del receptor de la lipoproteína de baja densidad; clofibrato, fenofibrato, y gemfirbozil; vitamina B6 y las sales de los mismos aceptables farmacéuticamente; vitamina B12; una vitamina antioxidante; un bloqueador β; un antagonista de la angiotensina II; un inhibidor de la enzima convertidora de angiotensina; un inhibidor de la aglutinación plaquetaria;; un antagonista del receptor de fibrinógeno; aspirina; fentiraminas, agonistas del receptor adrenérgico β3; sulfonilureas, biguanidas, inhibidores de α-glucosidasa, otros secretagogos de insulina, insulina y un agente hepatoprotector pueden usarse juntos para la preparación de una composición farmacéutica útil para los tratamientos descritos anteriormente.

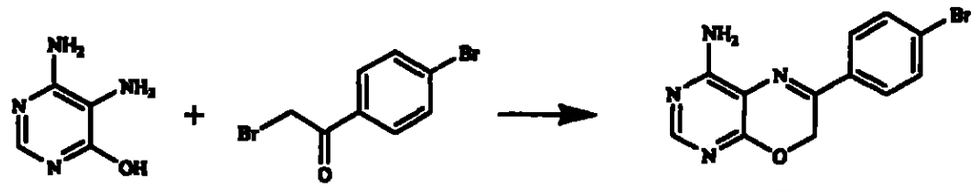
EJEMPLOS

Se registraron los espectros de ^1H NMR en un espectrómetro de NMR Varian Gemini 400 MHz, Jeol Alpha 300 MHz, Brucker DPX 300 MHz, Varian Mercury 400 MHz o Brucker Avance 500 MHz. Se tabularon los picos significativos y típicamente incluyen: número de protones, multiplicidad (s, singuleto; d, dupleto; t, tripleto; q, cuarteto; m, multipleto; br s, singuleto amplio) y constantes de acoplamiento en Hertz. Se registraron los espectros de IR en un Perkin Elmer 1600 FT-IR o un Perkin Elmer Spectrum One FT-IR. Los resultados de espectrometría de masa se reportaron como la proporción de la masa durante el cambio, seguido por la relativa abundancia de cada ión (entre paréntesis). Los materiales iniciales en los ejemplos de síntesis posteriores están disponibles ya sea de fuentes comerciales tales como Aldrich Chemical Co., Milwaukee, Wisconsin, USA, o vía los procedimientos de la literatura. Las abreviaciones usadas en los ejemplos siguientes tienen su significado aceptado en la literatura química. Por ejemplo, THF (tetrahidrofurano), Et_2O (éter dietílico), MeOH (metanol), LDA (litio diisopropilamida), MeCN (acetonitrilo), DMAP (4- dimetilaminopiridina), WSC (1- etil- 3- (3'-dimetilaminopropil)carbodiimida), HOBt (1. hidroxibenzotriazol), DBU (1, 6- diazabiciclo [5.4.0]undec-7-eno), DME (1, 2- dimetoxietano), DMF (N,N-dimetilformamida), DMSO (dimetil sulfoxida), AcOH (ácido

acético) y AcOEt (acetato de etilo. Se usaron en la presente otras abreviaciones convencionales: por ejemplo, un grupo metilo es a menudo suministrado como un "enlace" terminal no marcado, de conformidad con la práctica aceptada.

Ejemplo 1

Este ejemplo ilustra la preparación del compuesto designado Ej. 1.



Ej. 1

A una suspensión de 4, 5- diamino- 6- hidroxipirimidina (1.0 g, 7.93 mmoles) y bromuro de 4- bromofenacilo (2.2 g, 7.93 mmoles) en EtOH (20 ml) se añadió $NaHCO_3$ (666 mg, 7.93 mmoles), y la mezcla se agitó por 1.5 horas a 80 °C. Después de enfriar, la mezcla de reacción se concentró, y el residuo se diluyó con $CHCl_3$ (40 ml). Después de filtración del material insoluble, el filtrado se concentró. El residuo se trituró con tolueno para dar el compuesto deseado Ej. 1 (840 mg) como un cristal amarillo pálido, p.f.: > 200 °C. IR (cm^{-1}): 3291, 3145, 1634, 1586. MS (ESI+): 305, 307 (100).

^{1}H NMR (DMSO-d_6, 400 MHz): 5.44 (s, 2H), 7.10 (br s, 2H), 7.69 (d, 2H, J = 8.6 Hz), 7.93 (s, 1H), 8.03 (d, 2H, J = 8.6 Hz).

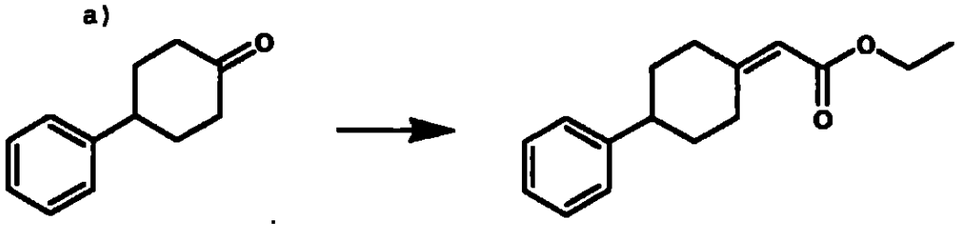
Ejemplos 1-2 a 1-37:

Los compuestos mostrados en la Tabla 1 se obtuvieron de la misma manera que en el Ejemplo 1.

Ejemplo 2

Este ejemplo ilustra la preparación del compuesto designado Ej. 2.

a)

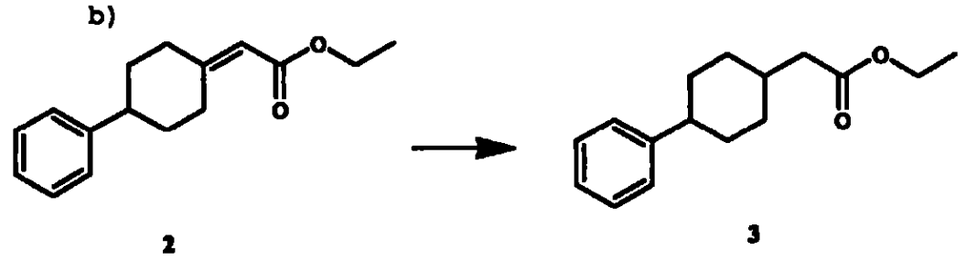


1 2

A 0 °C, una solución de fosfonoacetato de trietilo (2.6 ml, 12.9 mmoles) en DMF (5.5 ml), se añadió en porciones hidruro de sodio (50 % en aceite, 517 mg, 12.91 mmoles), y la mezcla de agitó a temperatura ambiente por 30 minutos. Se añadió una solución de 4-fenilciclohexanona en DMF (2.0 ml). Después de agitar por 0.5 horas, la mezcla se vertió en solución acuosa al 5 % de $KHSO_4$ (10 ml) y se extrajo con éter dietílico (10 ml). La capa orgánica se lavó sucesivamente con agua (5 ml) y salmuera (5 ml), se secó sobre $MgSO_4$ y se concentró. El residuo se purificó por cromatografía de columna

(hexano/AcOEt=7/1) para dar el compuesto 2 (2.0 g) como aceite incoloro.

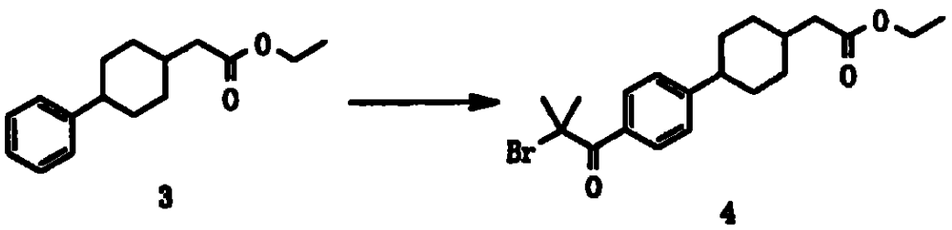
b)



2 3

A una solución agitada de 2 (500 mg, 2.05 mmoles) en EtOH (5 ml) se añadieron Pd/C al 10 % (50 mg). La mezcla se agitó a temperatura ambiente por 1 hora bajo una presión atmosférica de hidrógeno. Se retiró el catalizador por filtración, y le filtrado se concentró al vacío para producir el compuesto crudo 3 (491 mg) como aceite incoloro, el cual se usó en la siguiente reacción sin purificación adicional.

c)

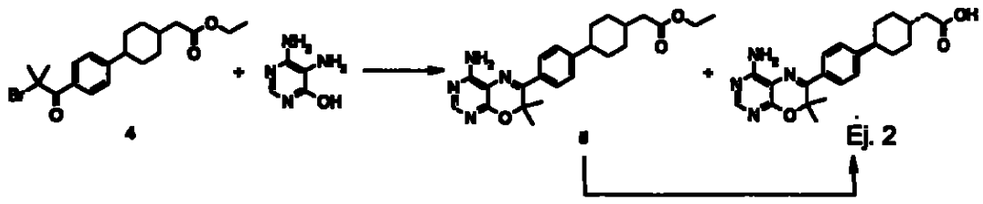


3 4

A 0 °C, a una solución del compuesto 3 (271 mg, 1.10 mmoles) en CH_2Cl_2 (1.4 ml), se añadió por porciones $AlCl_3$ anhidro (440 mg, 3.30 mmoles) y luego se añadió gota a gota bromuro de 2- bromoisobutirilo (0.14 ml, 1.10 mmoles). Después de agitar por 1 hora a 0 °C, la mezcla se

vertió en agua helada y se extrajo con $CHCl_3$ (5 ml). La capa orgánica combinada se lavó sucesivamente con solución saturada de $NaHCO_3$ (5 ml), se secó sobre $MgSO_4$ y se concentró. El residuo se purificó por cromatografía de columna (hexano/AcOEt= 7/1) para dar el Compuesto 4 (402 mg) como aceite incoloro.

d)

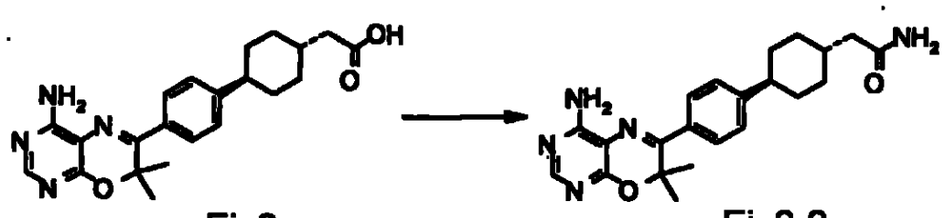


se mezcló 4, 5- diamino- 6- hidroxipirimidina (63.1 mg, 0.50 mmoles) con solución acuosa de HCl 1N (0.50 ml, 0.50 mmoles), agua (2 ml) y EtOH (2 ml) y el Compuesto 4 (395 mg, 1.00 mmoles) en EtOH (2 ml). La mezcla de reacción se reflujó (105 °C) por 12 horas. L mezcla de reacción se concentró a la mitad del volumen. El residuo se ajustó a pH de 9-10 con solución acuosa de NaOH 2N. La mezcla resultante se extrajo con AcOEt (5 ml). La capa acuosa se ajustó a pH de 3-4 con solución acuosa de ácido cítrico al 10 %, se extrajo con AcOEt (5 ml). La capa orgánica se lavó con agua (5 ml) y salmuera (5 ml), se secó sobre $MgSO_4$. La evaporación del solvente dio un Ej. 2 crudo (54 mg, mezcla de isómeros cis y trans). La primera capa orgánica se lavó con agua (5 ml) y salmuera (5 ml),

se secó sobre $MgSO_4$. La evaporación del solvente fió un Compuesto 5 crudo (126 mg, mezcla de isómeros cis y trans), el cual se usó para la siguiente reacción sin purificación adicional. a una solución de Compuesto 5 crudo en EtOH (1.2 ml), THF (1.8 ml) y agua (1.2 ml), se añadió solución acuosa de NaOH 2N (0.45 ml) después de agitar a 40 °C por 4 horas. La mezcla de reacción se concentró a la mitad de la cantidad en volumen, y se añadió agua (2 ml) y se lavó con AcOEt (2 ml). La capa acuosa de ajustó a pH de 3-4 con solución acuosa al 10 % de ácido cítrico, y se extrajo con AcOEt (5 ml). La capa orgánica se lavó con agua (5 ml) y salmuera (5 ml), se secó sobre $MgSO_4$. La evaporación del solvente dio un sólido blanco (113 mg). El sólido blanco (113 mg) y el Ejemplo 2 crudo se combinaron y se recristalizaron a partir de EtOH para dar el Ej. 2 (92 mg, de isómero trans) como un cristal blanco, p.f.: >270 °C. IR (cm-1): 3320, 2929, 1702, 1601. MS (ESI+): 395 (100).

^1H NMR (DMSO-d_6, 300 MHz): 1.10-1.16 (m, 2H), 1.45-1.84 (m, 13H), 2.15 (d, 2H, J=6.0 Hz), 2.54 (m, 1H), 6.97 (br s, 2H), 7.30 (d, 2H, J=8.4 Hz), 7.64 (d, 2H, J = 8.4 Hz), 7.94 (s, 1H), 11.95 (br s, 1H).

Ejemplo 2-2:

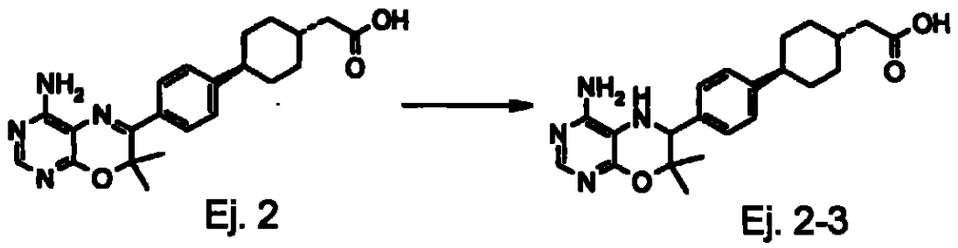


Ej. 2 Ej. 2-2

A una solución del Ejemplo 2 (80 mg, 0.20 mmoles) en DMF (2.4 ml) se añadió HOBt-H_2O (34.2 mg, 0.22 mmoles), EDC-HCl (42.8 mg, 0.22 mmoles) y solución acuosa de amoníaco al 28 % (0.04 ml, 0.81 mmoles). La mezcla de reacción se agitó a la temperatura ambiente por 70 horas. La mezcla se vertió en solución acuosa saturada de $NaHCO_3$ y se extrajo con AcOEt (3 ml). La capa orgánica fue lavada sucesivamente con agua (3 ml x 2), solución saturada de $NaHCO_3$ (3 ml) y salmuera (3 ml), se secó sobre $MgSO_4$. La evaporación del solvente dio un sólido blanco (69.5 mg). La mezcla fue fluidizada con EtOH para dar el Compuesto del Ejemplo 2-2 (48.2 mg) como un cristal blanco, p.f.: 224-226 °C. IR (cm^{-1}): 3348, 2923, 1672, 1604. MS (ESI+): 394 (100).

^1H NMR (DMSO-d_6, 400 MHz): 1.03- 1.22 (m, 8H), 1.4-1.49 (m, 2H), 1.70-1.82 (m, 5H), 2.14 (d, 2H, J=6.9 Hz). 2.54 (m, 1H), 4.11 (br s, 1H), 5.27 (br s, 1H), 6.23 (br s, 2H), 7.25 (d, 2H, J=8.0 Hz), 7.36 (d, 2H, J=8.0 Hz), 7.61 (s, 1H), 11.75 (br s, 1H).

Ejemplo 2-3:



Ej. 2 Ej. 2-3

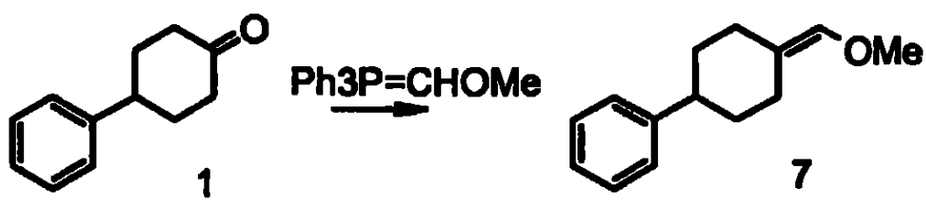
A una solución del Ejemplo 2 (120 mg, 0.30 mmoles) en THF (3.6 ml) y MeOH (3.6 ml), se añadió en porciones $NaBH_4$ (194 mg, 4.86 mmoles) y la mezcla de reacción se agitó a 0 °C por 20 horas. Se añadió solución acuosa 2 N de NaOH (0.46 ml, 0.91 mmoles) y se agitó por 30 minutos a 60 °C. La mezcla de reacción se concentró a la mitad de la cantidad en volumen. El residuo se añadió a agua (3 ml) y se lavó con AcOEt (3 ml). La capa acuosa se ajustó a pH de 3-4 con solución acuosa al 10 % de ácido cítrico, se extrajo con AcOEt (5 ml). La capa orgánica se lavó con agua (5 ml) y salmuera (5 ml), se secó sobre $MgSO_4$. La evaporación del solvente dio un sólido blanco (150 mg). El sólido se recristalizó a partir de EtOH para dar el Ej. 2-3 (97 mg) como un cristal blanco, p.f.: 274-279 °C (descompuesto). IR (cm^{-1}): 3414, 2927, 1650, 1595. MS (ESI+): 397 (100).

^1H NMR (DMSO-d_6, 300 MHz): 1.02-1.17 (m, 2H), 1.40-1.53 (m, 2H), 1.61 (s, 6H), 1.66-1.87 (m, 5H), 1.98 (d, 2H, J=7.1 Hz), 2.53(m, 1H), 6.67 (brs, 1H), 6.89 (br s,

2H), 7.21 (br s, 1H), 7.30 (d, 2H, J=8.1 Hz), 7.63 (d, 2H, J=8.1 Hz), 7.94 (s, 1H).

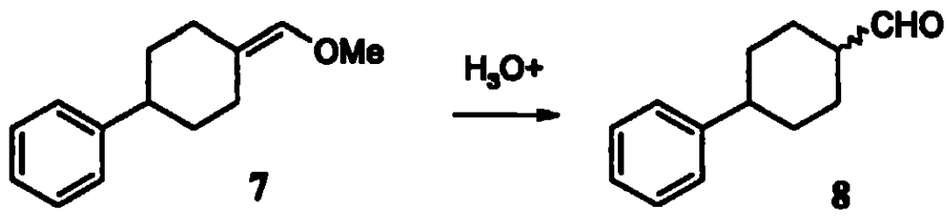
Ejemplo 2-4:

a)



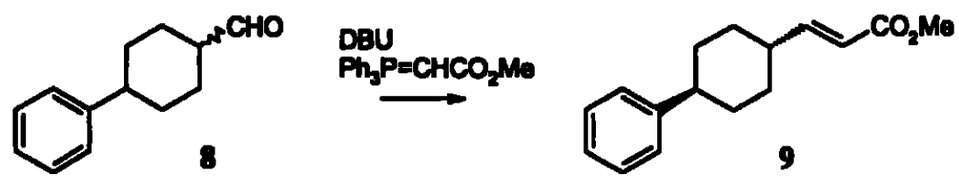
A una suspensión agitada de cloruro de metoximetiltrifenilfosfonio (3.14 g, 9.2 mmoles) en THF (8 ml) se añadió ter-butóxido de potasio (516 mg, 4.6 mmoles) bajo Ar. Después de 1 hora, se añadió a la solución 4-fenilciclohexanona (1) (400 mg, 2.3 mmoles). La mezcla se agitó por 1 hora a temperatura ambiente, se calentó toda la noche a 70 °C. Después de enfriamiento, la mezcla de reacción se vertió en solución acuosa saturada de $NaHCO_3$ (40 ml) y se extrajo con éter (50 ml). El extracto orgánico se lavó con agua (40 ml) y salmuera (40 ml) y se secó sobre Na_2SO_4, y el solvente se eliminó para dar el Compuesto 7 crudo (2.19 g), el cual se usó para la siguiente etapa sin purificación adicional.

b)



El Compuesto 7 crudo (2.19 g) se mezcló con solución acuosa al 80 % de AcOH (25 ml) y se calentó a 70 °C por 3.5 horas con agitación. La mezcla de reacción se concentró bajo presión reducida. El residuo se purificó por cromatografía de columna (hexano/AcOEt=20/1) para dar el Compuesto 8 (395 mg) como aceite incoloro.

c)



A una solución agitada de Compuesto 8 (383 mg, 2.03 mmoles) en tolueno (20 ml) se añadió DBU (365 µl, 2.44 mmoles) y la mezcla se calentó a 80 °C bajo Ar. Luego se añadió a la mezcla de reacción acetato de metil (trifenilfosforanilideno) (1.2 g, 3.05 mmoles) y la mezcla se agitó toda la noche a 100 °C. Después de enfriamiento la mezcla de reacción se lavó con solución al 5 % de $KHSO_4$ (10 ml), solución saturada de $NaHCO_3$ (10 ml) y salmuera (10 ml), y la capa orgánica se secó sobre Na_2SO_4 y se

concentró. El residuo se purificó por cromatografía de columna (hexano/AcOEt=20/1) para dar el Compuesto 9 (474 mg) como aceite incoloro.

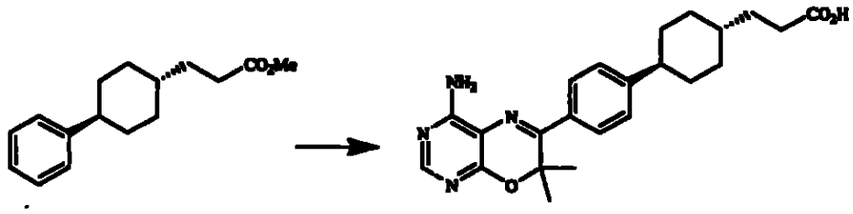
d)



9 10

Una suspensión de paladio al 10 % sobre carbón (50 mg) en una solución de Compuesto 9 (474 mg, 1.94 mmoles) en EtOH (15 ml) fue hidrogenada bajo la presión atmosférica de una atmósfera de hidrógeno toda la noche a temperatura ambiente. La mezcla de reacción se filtró, y el filtrado se concentró para dar el Compuesto 10 (436 mg) como un aceite incoloro, el cual fue suficientemente puro para ser usado para la siguiente etapa sin purificación adicional.

e)



10

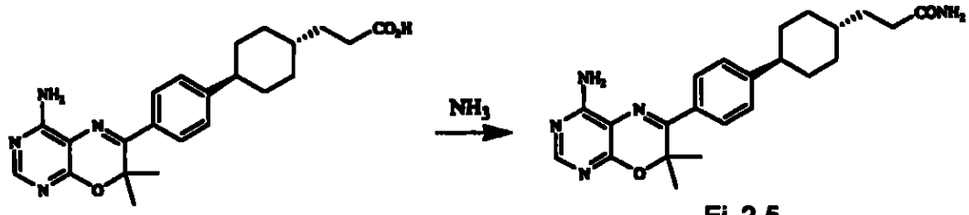
Ej. 2-4

El procedimiento del Ejemplo 2 se aplicó al Compuesto 10 en una escala de 436 mg (1.94 mmoles), produciendo Ej.

2-4 (231 mg) como un cristal incoloro, p.f.: > 250 °C. IR (cm^{-1}): 3310, 2922, 1702, 1611. MS (ESI+): 409 (100).

^1H NMR (DMSO-d_6, 400 MHz): 1.04-1.09 (m, 2H), 1.43 (m, 1H), 1.43-1.50 (m, 4H), 1.60 (s, 6H), 1.83 (br d, 4H, J=11.4 Hz), 2.25 (t, 2H, d=7.7 Hz), 2.50 (m, 1H), 6.88 (br s, 2H), 7.29 (d, 2H, J=8.3 Hz), 7.63 (d, 2H, J=8.3 Hz), 7.94 (s, 1H), 11.84 (br s, 1H).

Ejemplo 2-5:

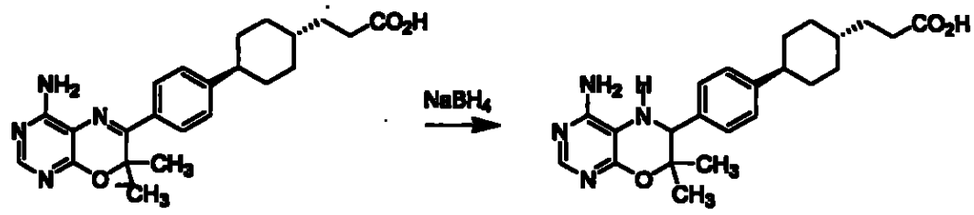


Ej. 2-4 Ej. 2-5

El procedimiento del Ejemplo 2-2 se aplicó al Ej. 2-4 en una escala de 50 mg (0.12 mmoles), produciendo el Ej. 2-5 (41 mg) como un cristal incoloro, p.f.: 244-246 °C. IR (cm-1): 3357, 29920, 1696, 1602. MS (ESI+): 408 (100).

^1H NMR (DMSO-d_6, 400 MHz): 1.04-1.08 (m, 2H), 1.29 (m, 1H), 1.40-1.49 (m, 4H), 1.60 (s, 6H), 1.83 (br d, 4H, J=10.2 Hz), 2.09 (t, 2H, d=7.4 Hz), 2.50 (m, 1H), 6.60 (br s, 1H), 6.88 (br s, 2H), 7.20 (br s, 1H), 7.29 (d, 2H, J=8.3 Hz), 7.63 (d, 2H, J=8.3 Hz), 7.94 (s, 1H).

Ejemplo 2-6:



Ej. 2-4 Ej. 2-6

El procedimiento del Ejemplo 2-3 se aplicó al Ej.2-4 en una escala de 38 mg (0.09 mmoles), produciendo el Ej. 2-6 (19 mg) como un cristal incoloro, p.f.: > 250 °C. IR (cm^{-1}): 3348, 2922, 1638, 1595. (MS(ESI+): 411(100).

^1H NMR(DMSO-d_6, 400 MHz): 1.04-1.09(m, 2H), 1.08 (s, 3H), 1.22 (s, 3H), 1.32 (m, 1H), 1.43-1.48 (m, 4H), 1.83 (br d, 4H, J=10.7 Hz), 2.24 (t, 2H, d=7.7 Hz), 2.50 (m, 1H), 4.11 (s, 1H), 5.26 (s, 1H), 6.22 (br s, 2H), 7.23 (d, 2H, J=8.1 Hz), 7.35 (d, 2H, J=8.1 Hz), 7.62 (s, 1H), 11.73 (br s, 1H)

Ejemplo 2-7:

a)

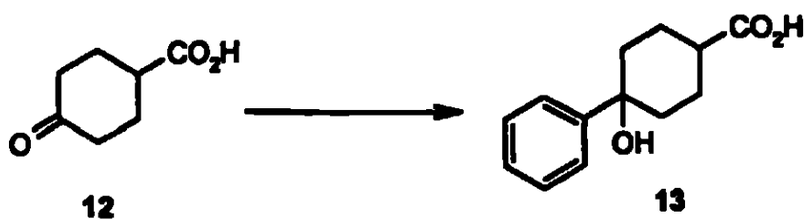


11 12

El Compuesto 11 (3 ml, 18.82 mmoles) y 30 ml de etanol y solución de NaOH fueron agitados juntos a temperatura ambiente por 3 horas. Luego se eliminaron los solventes al vacío, y se añadieron 12 ml de solución de

HCl 2M. La capa acuosa se extrajo con 25 ml de AcOEt, y el extracto se lavó con salmuera, se secó sobre $MgSO_4$, y se concentró al vacío para producir el Compuesto 12 crudo, el cual fue usado para la siguiente reacción sin purificación adicional.

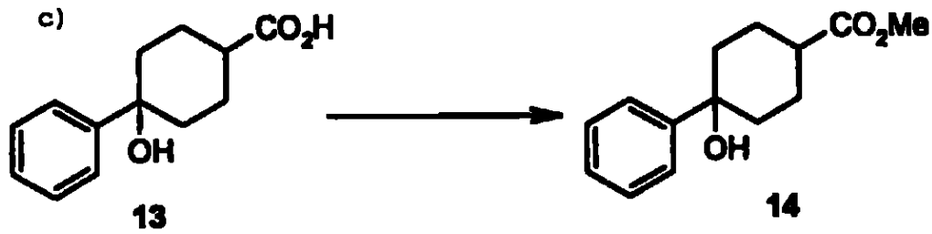
b)



12 13

A una solución agitada del Compuesto 12 crudo (1.594 g, aprox. 11.21 mmoles) en 15 ml de THF, se añadió PhMgBr 1.0 M (24.7 ml, 24.7 mmoles) a 0 °C y se agitó por 30 minutos. Después de adición de 10 ml de agua, la mezcla se acidificó con HCl 1M. La capa acuosa se extrajo con 30 ml de AcOEt, y el extracto se lavó con salmuera, se secó sobre $MgSO_4$, y se concentró al vacío para producir el Compuesto 13 crudo, el cual fue usado para la siguiente reacción sin purificación adicional.

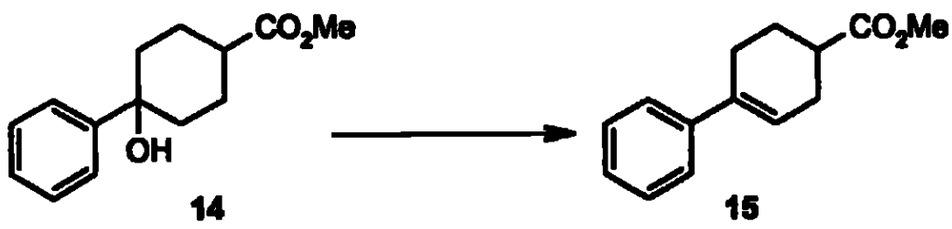
c)



13 14

A una suspensión agitada del Compuesto 13 crudo y K_2CO_3 (2.01 g, 14.5 mmoles) en 10 ml de DMF se añadió MeI (0.98 ml, 15.7 mmoles) y se agitó por 3 horas. Después de la adición de 15 ml de agua, la capa acuosa se extrajo con 25 ml de AcOEt, y el extracto se lavó con agua y salmuera, se secó sobre $MgSO_4$, y se concentró al vacío para producir el Compuesto 14 crudo, el cual se usó para la siguiente reacción sin purificación adicional.

d)



El Compuesto 14 crudo, 15 ml de $CHCl_3$, ácido trifluoroacético (3.02 ml, 39.4 mmoles) y trietilsilano (3.02 ml, 22.5 mmoles) se agitaron juntos a 65 °C por 5.5 horas. Después de adición de 25 ml de agua, se separó la capa orgánica, se lavó con salmuera, se secó sobre $MgSO_4$, y se concentró al vacío. El residuo se purificó por cromatografía de columna sobre gel de sílice (hexano/AcOEt=10/1), para dar el Compuesto 15 (1.5 g) como aceite amarillo.

e)



15 16

A una solución agitada del Compuesto 15 (1.5 g, 6.94 mmoles) en 15 ml de MeOH se añadió Pd/C al 10 % (240 mg). La mezcla se agitó a temperatura ambiente por 5 horas bajo una presión atmosférica de hidrógeno. Se eliminó el catalizador por filtración, y el filtrado se concentró al vacío para producir el Compuesto 16 crudo, el cual se usó para la siguiente reacción sin purificación adicional-

f)

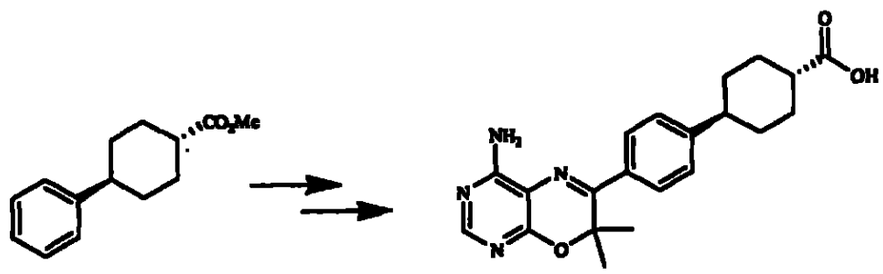


16 17

El Compuesto 16 crudo y 10 ml de MeOH y MeONa al 28 % (1.5 ml, 7.3 mmoles, solución metanólica) se agitaron juntos a 70 °C por 7.5 horas. Después de adición de 30 ml de agua, se extrajo la capa acuosa con 40 ml de AcOEt, y el extracto se lavó con agua y salmuera, se secó sobre $MgSO_4$, y se concentró al vacío para producir el Compuesto

17 crudo como una mezcla de diasterómeros (proporción (4:1), la cual fue usada para la siguiente reacción sin purificación adicional.

g)



17 Ej.2-7

El procedimiento del Ejemplo 2-c) y 2-d) se aplicó al Compuesto 17 en una escala de 69 mg (0.55 mmoles), produciendo el Ej. 2-7 (54 mg) como un cristal incoloro, p.f.: > 250 °C. IR (cm^{-1}): 3328, 2931, 1704, 1615. MS (ESI+): 381 (100).

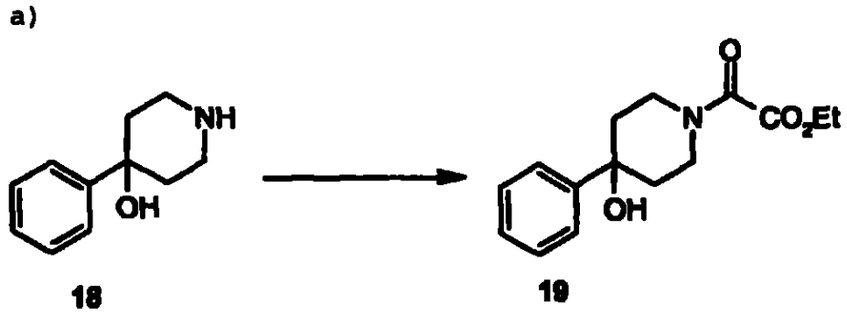
^1H NMR (DMSO-d_6, 400 MHz): 1.40- 1.58 (m, 4H), 1.61 (s, 6H), 1.82-1.92 (m, 2H), 1.97-2.08 (m, 2H), 2.24-2.36 (m, 1H), 2.52- 2.61 (m, 1H), 6.91 (br s, 2H), 7.31 (d, 2H, J=8.6 Hz), 7.65 (d, 2H, J=8.6 Hz), 7.95 (s, 1H), 11.92 (br s, 1H).

Ejemplo 2-8 a 2-268:

Los Compuestos mostrados en la Tabla 2 se obtuvieron de la misma manera que los Ejemplos 2 hasta 2-7.

Ejemplo 3

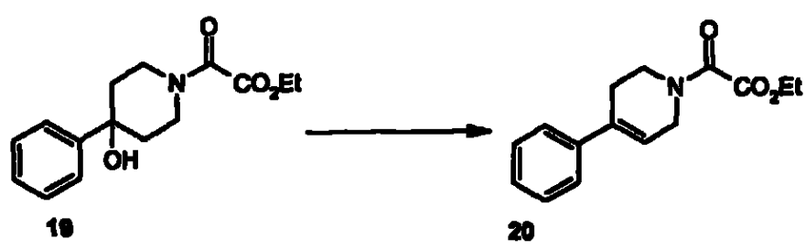
a)



18 19

A una solución agitada de 4-hidroxi-4-fenilpiperidina (18) (1.00 g, 5.64 mmoles) y Et_3N (0.94 ml, 6.77 mmoles) en 10 ml de $CHCl_3$ se añadió cloruro de etil oxalilo (0.63 ml, 5.64 mmoles) a 0 ° C y se agitó por 1 hora. Después de adición de 10 ml de agua, la capa orgánica se separó, se secó sobre $MgSO_4$, y se concentró al vacío para producir el Compuesto 19 crudo, el cual se usó para la siguiente reacción sin purificación adicional.

b)



19 20

El Compuesto 19 crudo, 10 ml de $CHCl_3$, ácido trifluoroacético (1.52 ml, 19.7 mmoles) y trietilsilano (1.52 ml, 11.3 mmoles) se agitaron juntos a 65 °C por 1.5 horas. Después de adición de 15 ml de agua, se separó la

capa orgánica, se lavó ccn salmuera, se secó sobre $MgSO_4$, y se concentró al vacío. El residuo se purificó por cromatografía de columna sobre gel de sílice (hexano/AcOEt=9/1) para dar el Compuesto 20 (1.38 g) como un aceite amarillo.

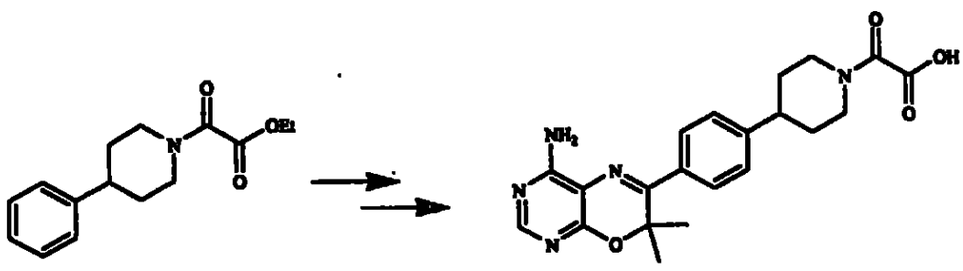
c)



20 21

A una solución agitada de Compuesto 20 (1.38 g, 5.32 mmoles) en 8 ml de MeOH se añadió Pd/C al 10 % (200 mg). La mezcla se agitó a temperatura ambiente por 5 horas bajo una presión atmosférica de hidrógeno. Se eliminó el catalizador por filtración, y el filtrado se concentró al vacío para producir el Compuesto 21 crudo, el cual se usó para la siguiente reacción sin purificación adicional.

d)



21 Ej. 3

El procedimiento del Ejemplo 2-c) y 2-d) se aplicó al

Compuesto 21 en una escala de 58 mg (0.46 mmoles), produciendo el Ej. 3 (20 mg) como un cristal incoloro, p.f.: 188.8 - 190.9 °C. IR (cm^{-1}): 1618, 1460, 1440. MS (ESI+): 410 (100).

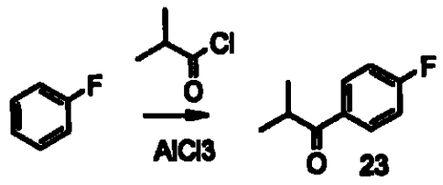
^1H NMR (DMSO-d_6, 400 MHz): 1.46- 1.67 (m, 2H), 1.6 (s, 6H), 1.81-1.94 (m, 2H), 2.72-2.98 (m, 2H), 3.21-3.34 (m, 1H), 3.63-3.71 (m, 1H), 4.34-4.46 (m, 1H), 6.98 (br s, 2H), 7.33 (d, 2H, J=8.4 Hz), 7.67 (d, 2H, J=8.4 Hz), 7.95 (s, 1H).

Ejemplo 3-2 a 3-3:

Los compuestos mostrados en la Tabla 3 se obtuvieron de la misma manera que en el Ejemplo 3.

Ejemplo 4

a)

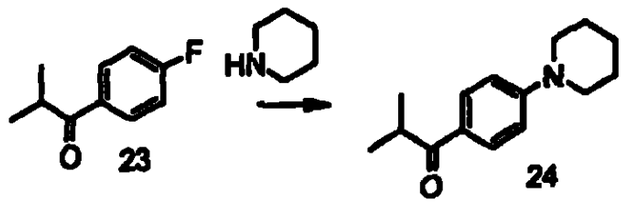


23

Se mezclaron bajo Ar fluorobenceno (1.78 ml, 18.96 mmoles), cloruro de aluminio (2.53 g, 18.96 mmoles) y cloruro de isobutirilo (1.0 ml, 9.48 mmoles) y la mezcla se agitó a temperatura ambiente por 1 hora. La mezcla de reacción se vertió en agua helada con agitación y se extrajo con éter (50 ml). El extracto orgánico se lavó con solución saturada de $NaHCO_3$ (30 ml) y salmuera (30 ml) y se secó sobre Na_2SO_4, y el solvente se eliminó para dar el

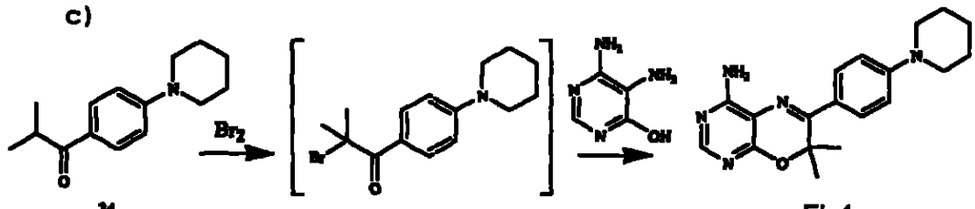
Compuesto 23 (1.47 g) como aceite incoloro, el cual fue suficientemente puro para ser usado para la siguiente etapa sin purificación adicional.

b)



A una solución del Compuesto 23 (50 mg, 0.30 mmoles) en DMSO (0.5 ml) se añadió piperidina (119 µl, 1.2 mmoles) y la mezcla se calentó a 140 °C por 5 horas bajo Ar. Después de enfriamiento la mezcla de reacción se diluyó con éter (10 ml) y se lavó con solución al 5 % de $KHSO_4$ (10 ml), agua (10 ml) y salmuera (10 ml). La capa orgánica se secó sobre Na_2SO_4, y el solvente se eliminó para dar el Compuesto 24 (65 mg) como aceite incoloro, el cual fue suficientemente puro para ser usado para la siguiente etapa sin purificación adicional.

c)



A una solución del Compuesto 24 (64 mg, 0.28 mmoles) en DME (1 ml) se añadieron sucesivamente HBr al 25 %- AcOH

(100 µl, 0.31 mmoles) y Br_2 (15.7 µl, 0.31 mmoles) y la mezcla se agitó a temperatura ambiente por 30 minutos. A la mezcla de reacción se añadió 4,5-diamino-6-hidroxipirimidina (17.5 mg, 0.14 mmoles), HCl 1N (140 µl, 0.14 mmoles), EtOH (1 ml), y agua (1 ml) y la mezcla se reflujó toda la noche. Después de enfriamiento se eliminó el EtOH bajo presión reducida, y el residuo se diluyó con AcOEt (10 ml) y se lavó con NaOH 1N (10 ml) y salmuera (10 ml). La capa orgánica se secó sobre Na_2SO_4 y se concentró. El residuo se purificó por cromatografía de capa fina usando como eluyente $CHCl_3$-MeOH (9:1) para producir el Ejemplo 4 (40 mg) como un cristal amarillo pálido, p.f.: 191-193 °C. IR (cm^{-1}): 3318, 2933, 1606, 158. MS (ESI+): 338 (100).

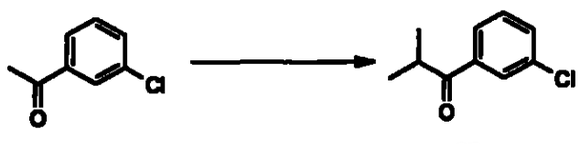
^1H NMR (DMSO-d_6, 400 MHz): 1.58-1.62 (m, 6H), 1.62 (s, 6H), 3.26 (br s, 4H), 6.79 (br s, 2H), 7.29 (d, 2H, J=9.0 Hz), 7.63 (d, 2H, J=9.0 Hz), 7.91 (s, 1H).

Ejemplo 4-2 a 4-7:

Los compuestos mostrados en la Tabla 4 se obtuvieron de la misma manera que en el Ejemplo 4.

Ejemplo 5

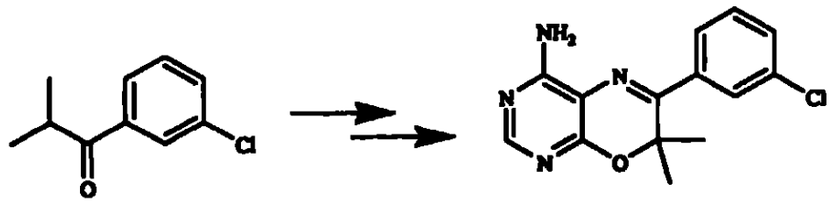
a)



27

3-Cloroacetofenona (0.5 ml, 3.85 mmoles), KOH pulverizado (2.16 g, 38.5 mmoles), 18-corona-6 (102 mg, 0.385 mmoles (102 mg, 0.385 mmoles), ioduro de metilo (1.92 ml, 30.8 mmoles) y 12 ml de tolueno se agitaron juntos a temperatura ambiente por 3 días. Después de adición de 30 ml de agua, la capa acuosa se extrajo con 20 ml de AcOEt, y el extracto se lavó con salmuera, se secó sobre $MgSO_4$, y se concentró al vacío para producir el Compuesto 27 crudo, el cual se usó para la siguiente reacción sin purificación adicional.

b)



27 Ej. 5

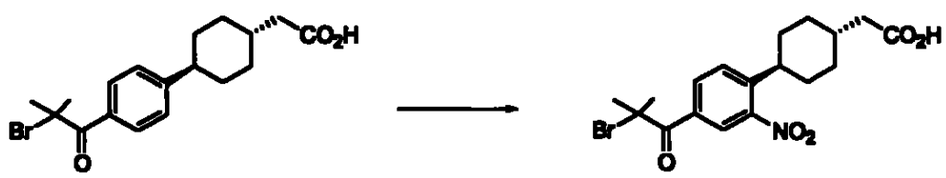
El procedimiento del Ejemplo 4 se aplicó al Compuesto 27 en una escala de 60 mg (0.47 mmoles), produciendo el Ejemplo 5 (40 mg) como un cristal incoloro, p.f.: 117.2-133.4 °C. IR (cm^{-1}): 1639, 1583, 1468. MS (ESI+).: 289 (100).

^1H NMR (DMSO-d_6, 400 MHz): 1.60 (s, 6H), 7.01 (br s, 2H), 7.48 (t, 1H, J=5.9 Hz), 7.55 (ddd, 1H, J=5.9, 1.3, 0.8 Hz), 7.67 (ddd, 1H, J=5.9, 1.3, 0.8 Hz), 7.76 (t, 1H, J=1.3 Hz), 7.97 (s, 1H).

Ejemplo 5-2 a 5-3:

Los compuestos mostrados en la Tabla 5 se obtuvieron de la misma manera que en el Ejemplo 5.

Ejemplo 6



22 28

A una solución agitada del Compuesto 22 (20.0 g, 54.5 mmoles) en 160 ml de $CHCl_3$ se añadió gota a gota ácido sulfúrico al 96 % (12.1 ml, 218 mmoles) y ácido nítrico al 60 % (4.56 ml, 59.9 mmoles) a 0 °C y se agitó a la misma temperatura por 30 minutos. La mezcla de reacción se vertió entonces en hielo triturado (150 g). La capa orgánica se lavó con agua (50 ml) y salmuera (50 ml), se secó sobre Mg_2SO_4, y se concentró al vacío. El residuo se purificó por cristalización a partir de AcOEt/Heptano (1/2, 120 ml), para dar el Compuesto 28 (18.4 g) como un cristal amarillo pálido.

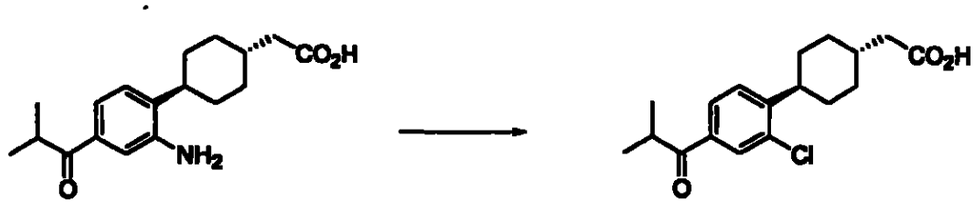
b)



28 29

A una suspensión agitada de Zn (15.9 g, 218 mmoles) en 150 ml de ácido acético, se añadió en porciones a 0 °C, y se agitó a la temperatura ambiente por 1 hora el Compuesto 28 (15.0 g, 36.4 mmoles), luego se agitó a 60 °C por otros 30 minutos. La mezcla se enfrió a temperatura ambiente, se filtró, y el filtrado se concentró al vacío. Al residuo se añadió AcOEt (150 ml), se lavó con agua (50 ml) y salmuera (50 ml), se secó sobre Mg_2SO_4, y se concentró al vacío. El residuo se purificó por cristalización a partir de $EtOH/H_2O$ (3/1, 50 ml), para dar el Compuesto 29 (9.36 g) como un cristal blanco.

c)



29 30

A una suspensión agitada de cloruro de cobre (II) (6.30 g, 44.5 mmoles) en 135 ml de acetona, se añadió nitrito de ter-butilo (5.88 ml, 44.5 mmoles) a 0 °C, luego se añadió en porciones el Compuesto 29 (9.00 g, 29.7 mmoles) y se agitó a la misma temperatura por 2 horas. Luego la mezcla se agitó a temperatura ambiente por 1 hora. Después de adición de HCl 2N, la mezcla se extrajo con AcOEt (100 ml). El extracto se lavó sucesivamente con

HCl 1N (50 ml), agua (50 ml), y salmuera (50 ml), se secó sobre $MgSO_4$, y se concentró al vacío. El residuo se purificó por cromatografía de columna sobre gel de sílice ($CHCl_3$/AcOEt=10/1~4/1) para dar el Compuesto 30 (7.40 g) como un cristal amarillo pálido.

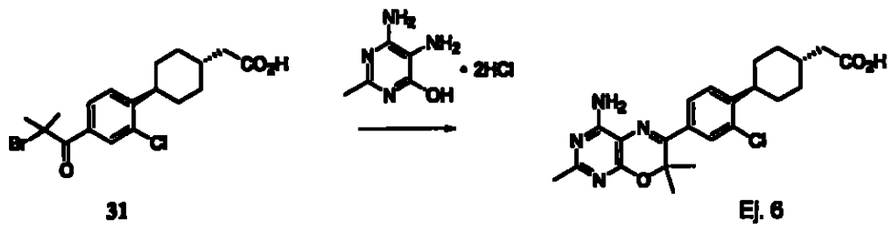
d)



30 31

A una solución agitada del Compuesto 30 (100 mg, 0.31 mmoles) en 1 ml de DME se añadió una solución de HBr al 25 %-AcOH (89 ml, 0.372 mmoles) y bromo (19 ml, 0.37 mmoles) a 0 °C y se agitó por 7 horas a temperatura ambiente. Después de adición de agua, la mezcla se extrajo con AcOEt, la capa orgánica se lavó con agua y salmuera, se secó sobre $MgSO_4$. La evaporación del solvente dio el Compuesto 31 crudo (112 mg) como un sólido amarillo pálido, el cual se usó para la siguiente reacción sin purificación adicional.

e)



31 Ej. 6

A una solución del Compuesto 31 (461 mg, 1.07 mmoles) en EtOH (4 ml) se añadió diclorhidrato de 4, 5- diamino- 6- hidroxi- 2- metilpirimidina (457 mg, 2.14 mmoles) y agua (1.3 ml), y se reflujó por 12 horas. Después de enfriamiento, a la mezcla de reacción se añadió NaOH 4N (2.5 ml, 10.0 mmoles) y se reflujó por 1 hora. Después de enfriamiento, la mezcla de reacción se ajustó a pH de 4 con HCl 4N y se agitó por 1 hora. El sólido depositado se colectó por filtración, se lavó con agua, y se secó al vacío para dar el Ejemplo 6 (354 mg) como un sólido naranja.

f)



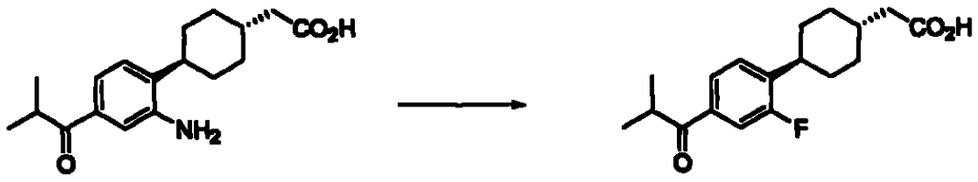
22 31

Una preparación alternativa de 31: A una solución agitada del Compuesto 22 (100 mg, 0.272 mmoles) en cloruro de sulfurilo (0.219 ml, 2.72 mmoles) se añadió cloruro de aluminio (127 mg, 0.953 mmoles) y la cantidad catalítica de S_2Cl_2 a 0 °C y se agitó por 2 horas. La mezcla de reacción se vertió entonces en agua helada (30 g) y se extrajo con AcOEt (30 ml). La capa orgánica se lavó con agua (20 ml), salmuera (20 ml), se secó sobre Mg_2SO_4. La

evaporación del solvente dio el Compuesto 31 crudo, el cual se usó para la siguiente reacción, sin purificación anterior.

Ejemplo 6-9:

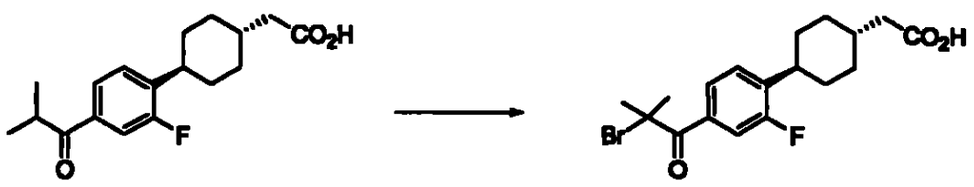
a)



29 32

A una suspensión del Compuesto 29 (1.0 g, 3.29 mmoles) en 15 ml de tolueno se añadió tetrafluoroborato de nitrosonio (462 mg, 3.95 mmoles) bajo argón a 0 °C. Después de agitar por 30 minutos a 0 °C, la mezcla se calentó a 120 °C y se agitó por 1 hora. Después de enfriamiento, la solución se diluyó con AcOEt, y la capa orgánica se lavó con agua, se secó sobre Na_2SO_4, y se concentró al vacío. El residuo se purificó por cromatografía de columna sobre gel de sílice (AcOEt/$CHCl_3$/hexano=1/1/1) para dar el Compuesto 32 (381 mg) como un cristal amarillo pálido.

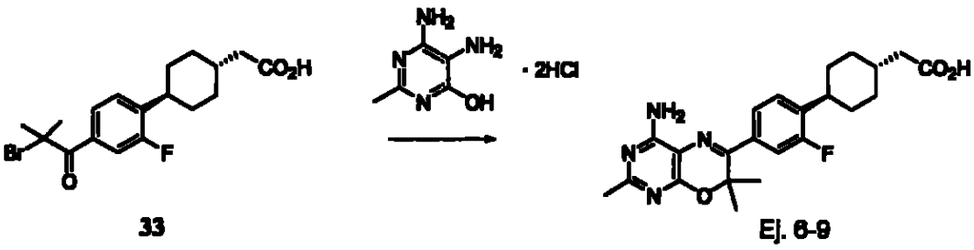
b)



32 33

A una solución agitada del Compuesto 32 (381 mg, 1.24 mmoles) en 4 ml de DME se añadió solución de HBr al 25 %-AcOH (356 ml, 1.49 mmoles) y bromo (76 ml, 1.49 mmoles) a 0 °C y se agitó por 5 minutos a 0 °C y por 30 minutos a temperatura ambiente. Después de adición de agua, la mezcla se extrajo con AcOEt, la capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4. La evaporación del solvente dio el Compuesto 33 crudo (454 mg) como un sólido amarillo pálido, el cual se usó para la siguiente reacción sin purificación adicional.

c)



33 Ej. 8-9

A una solución del Compuesto 33 (454 mg, 1.18 mmoles) en EtOH (6 ml) se añadió diclorhidrato de 4, 5- diamino- 6- hidroxi- 2- metil pirimidina (502 mg, 2.36 mmoles) y

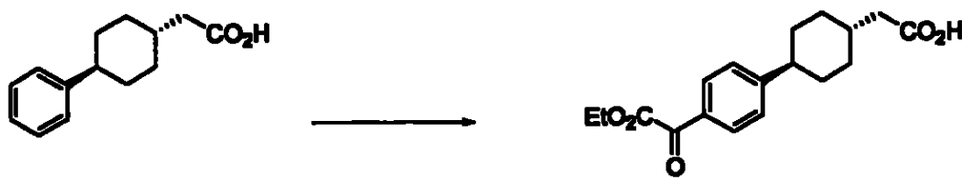
agua (2 ml), y se reflujó por 12 horas. Después de enfriamiento se añadió a la mezcla de reacción NaOH 2N (5.9 ml, 11.8 mmoles) y se reflujó por 3 horas. Después de enfriamiento, la mezcla de reacción se ajustó a pH de 4 con HCl 2N y se agitó por 1 hora. El sólido depositado se colectó por filtración, se lavó con agua, y se secó al vacío para dar el Ejemplo 6-9 (477 mg) como un sólido amarillo pálido.

Ejemplo 6-2 a 6-25:

Los compuestos mostrados en la Tabla 6, se obtuvieron de la misma manera que en los Ejemplos 6 y 6-9.

Ejemplo 7

a)



34 35

A una mezcla agitada de $AlCl_3$ (6.41 g, 48.1 mmoles) en 30 ml de CH_2Cl_2 se añadió cloruro de etil oxalilo (1.58 ml, 14.2 mmoles) y Compuesto 34 (3.0 g, 14.2 mmoles) a 0 °C y se agitó a 0 °C ~ temperatura ambiente por 2 horas. Después , la mezcla de reacción se vertió en hielo, se añadieron 10 ml de AcOEt a la mezcla y se añadió HCl concentrado hasta que la solución suspendida se volvió

clara. La capa orgánica se separó, y se concentró al vacío. El residuo se purificó por cromatografía de columna sobre gel de sílice (hexano/AcOEt=3/1~1/1) para dar el Compuesto 35 (3.36 g) como un sólido blanco.

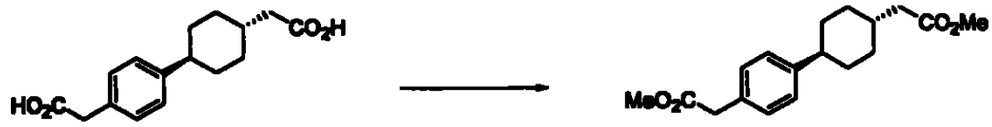
b)



35 36

La mezcla de Compuesto 35 (3.36 g, 10.5 mmoles) y KOH (2.0 g, 35.8 mmoles) y $N_2H_4.H_2O$ (1.38 ml, 28.5 mmoles) en tri(etilen glicol) (30 ml) se agitó a 175 °C por 1 hora. Después de enfriamiento a temperatura ambiente, se añadió HCl 2N (30 ml, 60 mmoles) y agua (40 ml) y se colectó el sólido depositado por filtración para dar el Compuesto 36 (2.58 g) como un sólido amarillo pálido.

c)

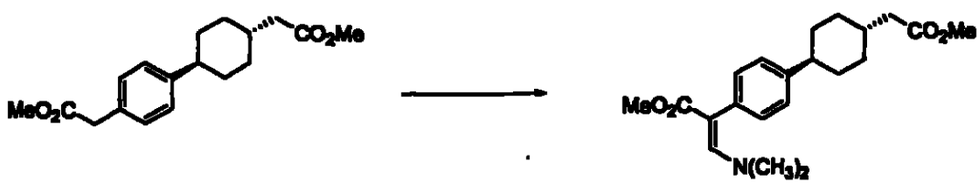


36 37

A una mezcla agitada de Compuesto 36 (2.57 g, 9.3 mmoles) en 30 ml de MeOH se añadió $SOCl_2$ (1.7 ml, 23.3 mmoles) a 0 °C y se agitó a temperatura ambiente por 4 horas. La mezcla de reacción se concentró al vacío, luego

el residuo se purificó por cromatografía de columna sobre gel de sílice (hexano/AcOEt=5/1~3/1) para dar el Compuesto 37 (2.13 g) como un sólido blanco.

d)



37 38

La mezcla de Compuesto 37 (2.13 g, 7.0 mmoles) y dietil acetal N, N-dimetilformamida (6.8 ml, 39.7 mmoles) se agitó a 130 °C por 3 días. Luego se añadió tolueno (20 ml) y la mezcla de reacción se concentró al vacío para dar el Compuesto 38 crudo, el cual se usó luego para la siguiente reacción sin purificación adicional.

e)



38 39

La mezcla de Compuesto 38 (crudo, 7.0 mmoles) y 4, 6-dihidroxi- 2- metilpirimidina (883 mg, 7.0 mmoles) en AcOH (20 ml) se agitó a 110 °C por 4 horas. Después la mezcla de reacción se concentró al vacío, se añadieron EtOH (10 ml) y agua (8 ml) y se colectaron por filtración los sólidos depositados para dar el Compuesto 39 (1.12 g) como

un sólido marrón.

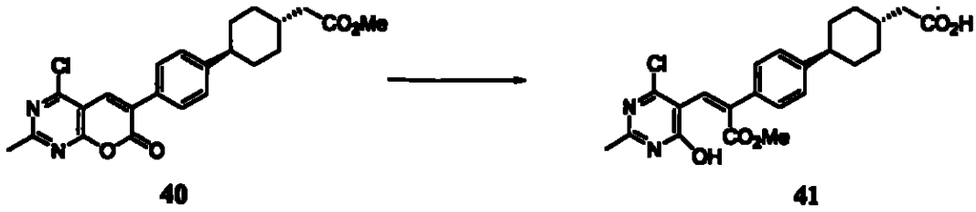
f)



39 40

La mezcla de Compuesto 39 (200 mg, 0.49 mmoles) y $POCl_3$ (1 ml) se agitó a 90 °C por 3 horas. Luego la mezcla de reacción se vertió en hielo y el producto se extrajo con AcOEt (3 ml), y la capa orgánica se lavó sucesivamente con agua (2 ml) y salmuera (2 ml). La capa orgánica se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se purificó por cromatografía de columna sobre gel de sílice (hexano/AcOEt=2/1) para dar el Compuesto 40 (174 mg) como un sólido naranja.

g)



40 41

La mezcla de Compuesto 40 m(124 mg, 0.30 mmoles) y NaOH 4N (0.41 ml, 1.65 mmoles) en MeOH (5 ml) se agitó a temperatura ambiente por 19 horas y luego se agitó a 60 °C por 2.5 horas. Después de enfriar a temperatura ambiente, se añadieron HCl 2N (2 ml, 4 mmoles) y agua (10 ml) y se

colectaron por filtración los sólidos depositados para dar el Compuesto 41 (100 mg) como un sólido amarillo pálido.

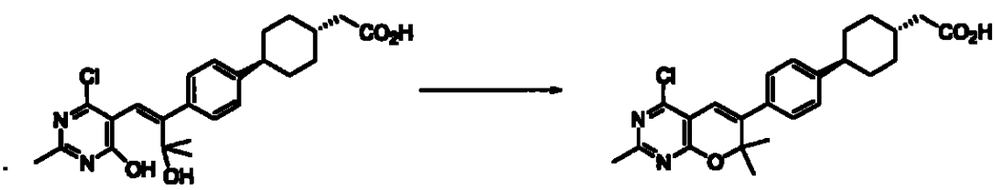
h)



41 42

A una solución agitada de MeMgBr 0.93 M en THF (1.2 ml, 1.12 mmoles) se añadió la solución suspendida de Compuesto 41 (100 mg, 0.23 mmoles) en THF (1.5 ml), y se agitó a temperatura ambiente por 3 horas. Después de adición de agua (1 ml) y HCl 2N (2 ml), el producto se extrajo con AcOEt (3 ml), y la capa orgánica se lavó sucesivamente con salmuera (2 ml). La capa orgánica se secó sobre $MgSO_4$, y se concentró al vacío para dar el Compuesto 42 crudo, el cual se usó entonces para la siguiente reacción sin purificación adicional.

i)

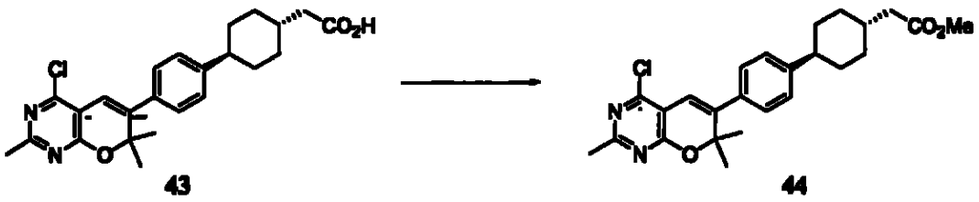


42 43

La mezcla de Compuesto 42 (crudo, 0.23 mmoles) y AcOH (2 ml) se agitó a 100 °C por 40 minutos. Después de enfriar a temperatura ambiente, se añadió agua (3 ml) a la

mezcla de reacción y el producto se extrajo con AcOEt (3 ml), luego la capa orgánica se lavó sucesivamente con agua (2 ml) y salmuera (2 ml). La capa orgánica se secó sobre $MgSO_4$ y se concentró al vacío. El residuo se purificó por cromatografía de columna sobre gel de sílice ($CHCl_3$/MeOH=40/1~20/1) para dar el Compuesto 43 (54 mg) como un sólido naranja.

j)



43 44

A una suspensión agitada de Compuesto 43 (52 mg, 0.12 mmoles) y K_2CO_3 (50 mg, 0.37 mmoles) en DMF (1.5 ml) se añadió MeI (0.023 ml, 0.37 ml), y la mezcla se agitó a temperatura ambiente por 3 horas. Después de adición de agua (3 ml), el producto se extrajo con AcOEt (3 ml), y la capa orgánica se lavó sucesivamente con agua (2 ml) y salmuera (2 ml). La capa orgánica se secó sobre $MgSO_4$, y se concentró al vacío. El residuo se purificó por cromatografía de columna sobre gel de sílice (Hexano/AcOEt=4/1) para dar el Compuesto 44 (46 mg) como un sólido blanco.

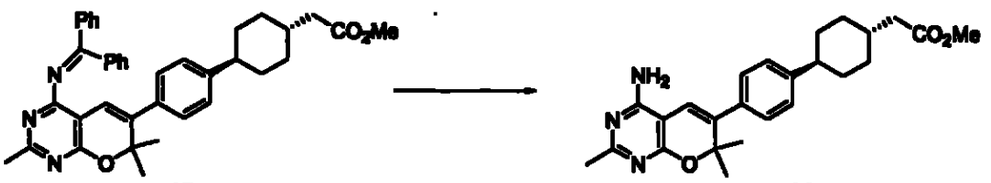
k)



44 45

A una solución agitada de Compuesto 44 (134 mg, 0.30 mmoles) en tolueno (4 ml) se añadió benzofenona imina (0.255 ml, 1.52 mmoles) y $Pd(OAc)_2$ (14 mg, 0.061 mmoles) y (S)-(-)BINAP (57 mg, 0.091 mmoles) y $CsCO_3$ (198 mg, 0.61 mmoles), y la mezcla se agitó a 110 °C por 23 horas. Después de adición de agua (3 ml), el producto se extrajo con AcOEt (3 ml), y la capa orgánica se lavó sucesivamente con salmuera (2 ml). La capa orgánica se secó sobre $MgSO_4$, y se concentró al vacío. El residuo se purificó por cromatografía sobre gel de sílice (Hexano/AcOEt=4/1~2/1) para dar el Compuesto 45 (88 mg) como un sólido amarillo.

l)

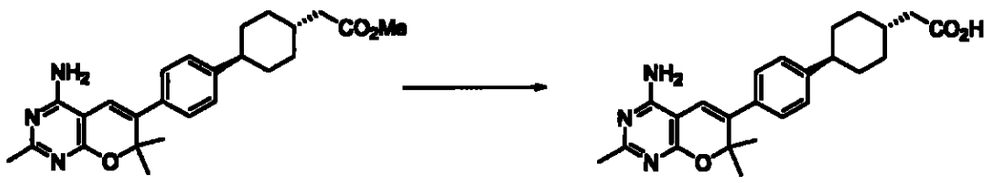


45 46

A una solución agitada de Compuesto 45 (85 mg, 0.145 mmoles) en THF (2 ml) se añadió HCl conc. (0.050 ml), y la mezcla se agitó a temperatura ambiente por 1 hora. Después

de adición de NaOH 4N (0.14 ml), el producto se extrajo con AcOEt (5 ml), y la capa orgánica se lavó sucesivamente con agua (4 ml) y salmuera (4 ml). La capa orgánica se concentró al vacío, el residuo así obtenido se purificó por cromatografía de columna sobre gel de sílice ($CHCl_3$/MeOH=50/1) para dar el Compuesto 46 (57 mg) como un sólido.

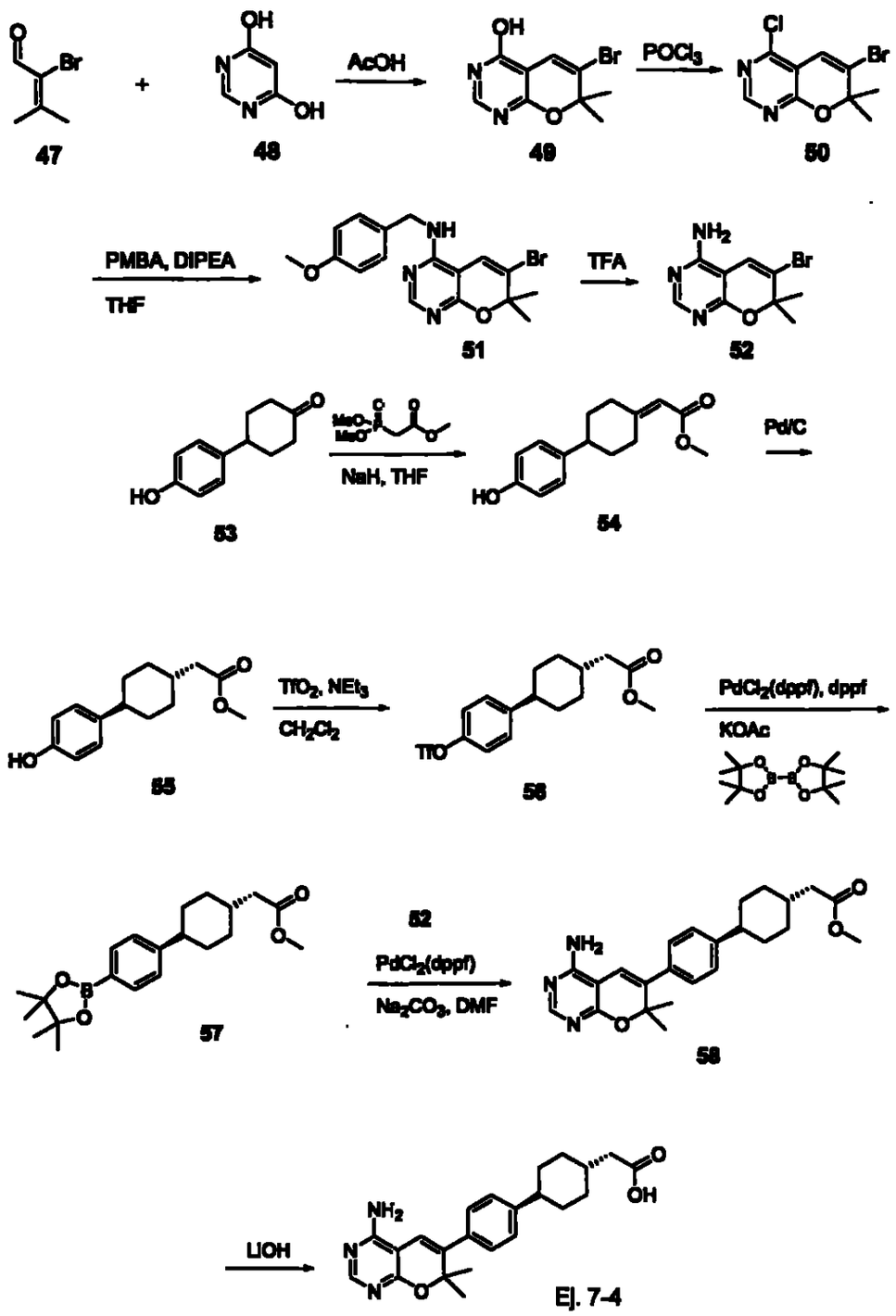
m)



46 Ej. 7

A una mezcla agitada de Compuesto 46 (55 mg, 0.13 mmoles) en solvente mezclado (2 ml de THF y 3 ml de MeOH) se añadió NaOH 1 N (0.43 ml, 0.43 mmoles), y la mezcla se agitó a 80 °C por 4 horas. Después la mezcla de reacción se concentró al vacío, se añadieron a la mezcla HCl 2N (0.25 ml, 0.5 mmoles) y EtOH (1 ml) y los sólidos depositados se colectaron por filtración para dar el Ejemplo 7 (38 mg) como un sólido amarillo pálido.

Ejemplo 7-4:


Br
OH
OH
AcOH
OH
Br
POCl3
Cl
Br
47
48
49
50
PMBA, DIPEA
THF
NH
Br
TFA
NH2
Br
51
52
HO
MeO
MeO
NaH, THF
HO
Pd/C
53
54
HO
Tf2O, NEt3
CH2Cl2
TfO
PdCl2(dppf), dppf
KOAc
55
56
57
52
PdCl2(dppf)
Na2CO3, DMF
NH2
58
LiOH
NH2
OH
Ej. 7-4

Compuesto 49.Una mezcla de 47 (10.0 g, 89.2 mmoles) y 48 (14.5 g, 89.2 mmoles) en AcOH (100 ml) se calentó a 100 °C por 24 horas. Se eliminó el solvente al vacío y el residuo marrón resultante se purificó por cromatografía instantánea (gel de sílice $MeOH/CH_2Cl_2$ al 4 %) para proporcionar 49 como un sólido amarillo (12.04 g).

^1H NMR (DMSO-d_6) δ 8.02 (s, 1H), 6.71 (s, 1H), 1.53 (s, 6H). Espectro de Masa (ESI+) m/e = 257 y 259 (M+1).

Compuesto 50. Una solución de 49 (2.13 g, 8.29 mmoles) en $POCl_3$ (10 ml) se calentó a 100 °C por 1 hora, se enfrió a temperatura ambiente, y se vertió sobre hielo. La solución resultante se extrajo con EtOAc (3 x 75 ml). Se conjuntaron las capas orgánicas, se lavaron con salmuera, se secaron ($MgSO_4$), se filtró, y se concentró al vacío para proporcionar 50 como un aceite amarillo (2.28 g).

^1H NMR (DMSO-d_6) δ 8.49 (s, 1H), 7.00 (s, 1H), 1.64 (s, 6H). Espectro de Masa (ESI+) m/e = 275, 277, y 279 (M+1).

Compuesto 51. Se añadió Diisopropiletilamina (1.9 ml, 10.9 mmoles) a una solución de 50 (2.0 g, 7.26 mmoles) y 4- metoxibencilamina (2.83 ml, 21.8 mmoles) en THF (20 ml). La mezcla de reacción se calentó a reflujo por 16 horas, se enfrió a temperatura ambiente, se diluyó con agua (20 ml) y se extrajo con EtOAc (3 x 75 ml). Las capas orgánicas se conjuntaron, se lavaron con salmuera, se

secaron ($MgSO_4$), se filtraron, y se concentraron al vacío para proporcionar un sólido amarillo. La purificación por cromatografía instantánea (gel de sílice, EtOAc/hexano al 50 %) proporcionó 51 como un sólido blancuzco (2.14 g).

^1H NMR (DMSO-d_6) δ 8.05 (s, 1H), 7.79 (m, 1H), 7.21 (d, J = 8.7 Hz, 2H), 7.08 (s, 1H), 6.87 (d, J= 8.7 Hz, 2H), 4.50 (d, J = 5.7 Hz, 2H), 3.71 (s, 3H), 1.50 (s, 6H). Espectro de Masa (ESI+) m/e = 376, y 378 (M+1).

Compuesto 52. Una solución de 51 (620 mg, 1.65 mmoles) en TFA (20 ml) se calentó a 50 °C por 7 horas. Se eliminó el solvente al vacío y el aceite resultante se disolvió en EtOAc (30 ml), se lavó con solución acuosa saturada de $NaHCO_3$ (2 x 50 ml), salmuera, se secó ($MgSO_4$), se filtró, y se concentró al vacío para proporcionar un sólido amarillo. Se sonicó el sólido en Et_2O (5 ml) y se colectó por filtración al vacío para proporcionar 52 como un sólido blancuzco (388 mg).

^1H NMR (DMSO-d_6) δ 7.97 (s, 1H), 7.10 (s, 1H), 7.00 (s, 2H), 1.52 (s, 6H). Espectro de masa (ESI+) m/e = 256 y 258 (M+1).

Compuesto 54. una suspensión al 60 % en aceite mineral de NaH (211 mg, 5.23 mmoles) se añadió a una solución de 53 (1.0 g, 5.26 mmoles) en THF anhidro (25 ml) a 0 °C bajo una atmósfera de nitrógeno. En un matraz separado se añadió fosfonoacetato de trimetilo (1.02 ml,

6.31 mmoles) a una suspensión de NaH (315 mg, 7.88 mmoles) en THF anhidro (25 ml) a 0 °C bajo una atmósfera de nitrógeno. Después de 15 minutos, las dos mezclas se calentaron a temperatura ambiente y se agitó por 30 minutos. La solución que contiene la cetona se añadió a la solución de fosfonato vía cánula. Se agitó la mezcla de reacción a temperatura ambiente, se detuvo la reacción con agua (50 ml) y se extrajo con EtOAc (3 x 50 ml). Se conjuntaron las capas orgánicas, se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y concentraron al vacío para proporcionar 54 como un sólido amarillo (1.25 g).

^1H NMR (DMSO-d_6) δ 9.12 (s, 1H), 7.01 (d, J=8.4 Hz, 2H), 6.66 (d, J = 8.4 Hz, 2H), 5.70 (s, 1H), 3.82 (m, 1H), 3.62 (s, 3H), 2.70 (m, 1H), 2.33 (m, 2H), 2.01 (m, 1H), 1.92 (m, 2H), 1.47 (m, 2H). Espectro de Masa (ESI+) m/e = 247 (M+1).

Compuesto 55. Una mezcla de 54 (5.18 g, 21.0 mmoles) y Pd/C al 10 % (500 mg) en EtOAc (150 ml) se agitó a temperatura ambiente bajo una atmósfera de hidrógeno por 20 horas. La mezcla de reacción se filtró a través de Celite y se concentró al vacío para proporcionar un sólido amarillo. La recristalización a partir de EtOAc (6 ml) proporcionó 55 como prismas incoloros con una proporción de 20:1 de trans/cis (2.96 g).

^1H NMR (DMSO-d_6) δ 9.08 (s, 1H), 6.99 (d, J= 8.5 Hz,

2H), 6.65 (d, J = 8.5 Hz, 2H), 3.60 (s, 3H), 2.33 (dt, J = 3.0 y 12.1 Hz, 1H), 2.23 (d, J = 6.9 Hz, 2H), 1.75 (m, 5H), 1.38 (m, 2H) 1.11 (m, 2H). Espectro de Masa (ESI+) m/e = 249 (M+1).

Compuesto 56. Se añadió gota agota trietilamina (421 µl, 3.02 mmoles) a una solución de 55 (500 mg, 2.02 mmoles) y anhídrido trifluorometansulfónico (424 µl, 2.52 mmoles) en CH_2Cl_2 anhidro (20 ml) a 0 °C bajo una atmósfera de nitrógeno. La mezcla de reacción se calentó a temperatura ambiente y se agitó por 4.5 horas, se vertió en agua (30 ml)y las capas se separaron. Las capas orgánicas se conjuntaron, se lavaron con solución acuosa saturada de $NaHCO_3$, salmuera, se secaron ($MgSO_4$), se filtraron, y se concentraron al vacío para proporcionar 56 como un sólido blancuzco (765 mg).

^1H NMR (DMSO-d_6) δ 7.42 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 3.60 (s, 3H), 2.57 (m, 1H), 2.25 (d, J = 6.6 Hz, 2H), 1.79 (m, 5H), 1.47 (m, 2H), 1.14 (m, 2H). Espectro de Masa (ESI+) m/e = 381 (M+1).

Compuesto 57. Un matraz de fondo redondo de 50 ml se cargó con 56 (1.35 g, 3.55 mmoles), KOAc (1.05 g, 10.6 mmoles), bis(pinacolato)diboro (991 mg, 3.90 mmoles), $PdCl_2$(dppf) (87 mg, 0.107 mmoles), y dppf (59 mg, 1.07 mmoles). El matraz se llenó consecutivamente con nitrógeno y se evacuó tres veces. Se añadió dioxano anhidro (25 ml)

y la mezcla de reacción se calentó a 80 °C por 17 horas. La mezcla de reacción se enfrió a temperatura ambiente, se diluyó con EtOAc (50 ml), se lavó con salmuera, se secó ($MgSO_4$), se filtró, y se concentró al vacío para proporcionar un aceite marrón. La purificación por cromatografía instantánea (gel de sílice, EtOAc/hexano) ¡ al 15 % proporcionó 57 como un sólido blanco (914 mg).

^1H NMR (DMSO-d_6) δ 7.59 (d, J = 7.8 Hz, 2H), 7.24 (d, J = 7.9 Hz, 2H), 3.60 (s, 3H), 2.45 (m, 1H), 2.25 (d, J = (d, J = 6.8 Hz, 2H), 1.78 (m, 5H), 1.46 (m, 2H), 1.28 (s, 12H), 1.14 (m, 2H). Espectro de Masa (ESI+) m/e = 359 (M+1).

Compuesto 58. Una mezcla de 52 (1.12 g, 4.38 mmoles), 57 (2.0 g, 6.57 mmoles), $PdCl_2$ (dppf) (107 mg, 0.132 mmoles) y solución acuosa 2 M de Na_2CO_3 (11 ml) en DMF (30 ml) se calentó a 80 °C bajo una atmósfera de nitrógeno por 24 horas. La solución se diluyó con agua (75 ml) y se colectó el precipitado resultante por filtración al vacío para proporcionar un sólido blancuzco. La purificación por cromatografía instantánea (gel de sílice, MeOH al 5 % / CH_2Cl_2) proporcionó 58 como un sólido blanco (1.09 g).

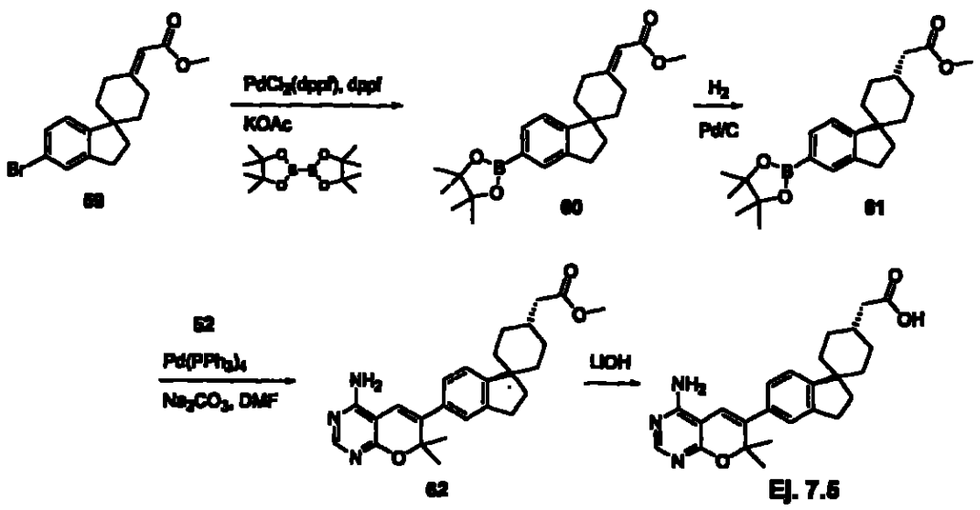
^1H NMR (DMSO-d_6) δ 7.95 (s, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 6.86 (s, 2H), 6.57 (s, 1H), 3.61 (s, 3H), 2.47 (m, 1H), 2.25 (d, J=6.7 Hz, 2H), 1.79 (m, 5H), 1.51 (s, 6H), 1.44 (m, 2H), 1.16 (m, 2H).

Espectro de Masa (ESI+) m/e = 408.5 (M+1).

Ejemplo 7-4. Una solución de 58 (130 mg, 0.319 mmoles) en MeOH (12 ml) y solución acuosa al 10 % LiOH (4 ml) se calentó a 100 °C por 4 horas. Se eliminó el MeOH al vacío y la solución acuosa resultante se acidificó con HCl 1N a pH de 4. El precipitado resultante se colectó por filtración al vacío para proporcionar el Ejemplo 7-4 como un sólido blancuzco (111 mg).

^{1}H NMR (DMSO-d_6) δ 8.09 (s, 1H), 7.33 (bs, 2H), 7.30 (d, J=8.1 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 6.61 (s, 1H), 2.47 (m, 1H), 2.15 (d, J= 6.9 Hz, 2H), 1.82 (m, 4H), 1.74 (m, 1H), 1.55 (s, 6H), 1.51 (m, 2H), 1.13 (m, 2H). Espectro de Masa (ESI+) m/e = 394 (M+1).

Ejemplo 7-5:



Compuesto 60. Un matraz de fondo redondo de 100 ml se cargó con 59 (2.54 g, 7.56 mmoles), bis (pinacolato) de

diboro (2.41 g, 9.47 mmoles), KOAc (2.23 g, 2.27 mmoles), $PdCl_2$ (dppf) (186 mg, 0.227 mmoles), y dppf (126 mg, 0.227 mmoles). El matraz se llenó consecutivamente con nitrógeno y se evacuó tres veces. Se añadió dioxano anhidro (70 ml) y la mezcla de reacción se calentó a 80 °C por 17 horas. La mezcla de reacción se diluyó con EtOAc (75 ml) y se lavó con agua helada, salmuera, se secó ($MgSO_4$), se filtró, y se concentró al vacío para proporcionar un aceite marrón. La purificación por cromatografía instantánea (gel de sílice, EtOAc al 5 %/hexano) proporcionó 60 como un sólido blanco (2.02 g).

^1H NMR (DMSO-d_6) δ 7.52 (s, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 5.74 (s, 1H), 3.71 (m, 1H), 3.62 (s, 3H), 2.89 (t, J = 7.4 Hz, 2H), 2.41 (m, 1H), 2.32 (m, 1H), 2.13 (m, 3H), 1.66 (m, 4H), 1.28 (s, 12H). Espectro de Masa (ESI+) m/e = 383 (M+1).

Compuesto 61. Una mezcla de 60 (2.02 g, 5.28 mmoles) y Pd al 10 %/C (562 mg) en MeOH (50 ml) se agitó a temperatura ambiente bajo una atmósfera de nitrógeno por 21 horas. La mezcla de reacción se filtró a través de celita y se concentró al vacío para proporcionar un aceite incoloro. La cristalización a partir de MeOH, seguida por recristalización a partir de CH_2Cl_2 con difusión en MeOH proporcionó 61 como agujas blancas con una proporción de 20:1 de trans/cis (600 mg).

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^{1}H NMR (DMSO-d_6) δ .70 (s, 1H), 7.68 (d, J = 7.7 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 3.71 (s, 3H), 2.90 (t, J = 7.3 Hz, 2H), 2.29 (d, J = 7.0 Hz, 2H), 1.99 (t, J = 7.4 Hz, 2H), 1.90 (m, 1H), 1.76 (m, 2H), 1.68 (m,2H), 1.60 (m, 2H), 1.35 (s, 12H), 1.25 (m, 2H). Espectro de masa(ESI+) m/e = 385 (M+1).

Compuesto 62. Una mezcla de 52 (100 mg, 0.391 mmoles) 61 (150 mg, 0.381 mmoles), $Pd(PPh_3)_4$ (23 mg, 0.020 mmoles), y solución acuosa 2 M de Na_2CO_3 (1 ml) en DMF (10 ml) se calentó a 80 °C por 3 horas. La mezcla de reacción se diluyó con EtOAc (75 ml), se lavó con agua (3 x 50 ml), salmuera, se secó ($MgSO_4$), se filtró, y se concentró al vacío para proporcionar un sólido amarillo. La purificación por cromatografía instantánea (gel de sílice, MeOH al 5 %/CH_2Cl_2) proporcionó 62 como un sólido blanco (103 mg).

^{1}H NMR (DMSO-d_6) δ 7.95 (s, 1H). 7.18 (m, 3H), 6.84 (s, 2H), 6.56 (s, 1H), 3.61 (s, 3H), 2.85 (t, J = 7.3 Hz, 2H), 2.28 (d, J = 7.0 Hz, 2H), 1.95 (t, J = 7.3 Hz, 2H), 1.79 (m, 1H), 1.65 (m, 5H), 1.51 (s, 6H), 1.49 (m, 1H), 1.23 (m, 2H). Espectro de Masa (ESI+) m/e = 434 (M+1).

Ejemplo 7-5. Una solución de 62 (103 mg, 0.238 mmoles) en MeOH (9 ml) y sclución acuosa al 10 % de LiOH (3 ml) se calentó a 100 °C por 2 horas. Se eliminó el MeOH al vacío y la capa acuosa resultante se acidificó a pH de

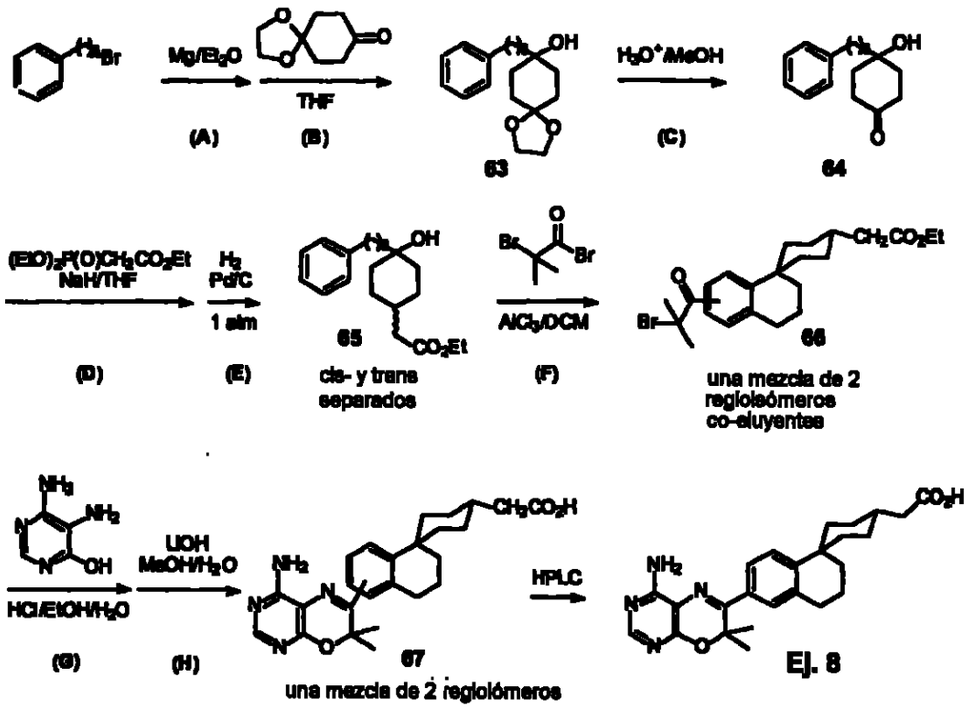
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1 con HCl 1N. El precipitado resultante se colectó por filtración al vacío para proporcionar el Ejemplo 7-5 como un sólido blancuzco (73 mg).

^{1}H NMR (DMSO-d_6) δ 8.14 (s, 1H), 7.50 (bs, 2H), 7.20 (m, 3H), 6.61 (s, 1H), 2.86 (t, J = 7.2 Hz, 2H), 2.17 (d, J = 6.8 Hz, 2H), 1.96 (t, J = 7.3 Hz, 2H), 1.71 (m, 1H), 1.67 (m, 2H), 1.63 (m, 3H), 1.56 (s, 6H), 1.50 (m, 2H), 1.22 (m, 2H). Espectro de Masa (ESI+) m/e = 420 (M+1).

Los compuestos mostrados en la Tabla 7 se obtuvieron de la misma manera que en los Ejemplos 7, 7-4 y 7-5.

Ejemplo 8



Etapas (A), (B) y (C). En un matraz de fondo redondo de 3 cuellos secado a la flama equipado con un agitador magnético, un condensador de reflujo y un embudo de adición se colocó magnesio, agitando (1.1 equivalentes, 8.8 g) y éter dietílico (60 ml) bajo una atmósfera de nitrógeno. Se añadió una solución en éter dietílico de 1-bromo. 3- fenilpropano (322.4 mmoles, 65.5 g) se añadió vía un embudo de adición a una velocidad tal que un reflujo lento se mantuvo en el transcurso de la adición, aproximadamente 1 hora 10 minutos. Unas cuantas partículas de yodo fueron introducidas al comienzo de la adición para iniciar la reacción. Después de la terminación de la adición del bromo, la mezcla de reacción se calentó a reflujo por 1 hora, se dejó enfriar a temperatura ambiente y se enfrió adicionalmente en un baño de hielo. Se añadió lentamente a la mezcla enfriada con hielo, una solución de monoetilen cetal 1, 4- ciclohexanodiona (1 equivalente, 51.91 g) en THF (100 ml) vía el embudo de adición con agitación durante 1 hora 30 minutos.

La mezcla se agitó continuamente por 30 minutos, en el baño de hielo y toda la noche a temperatura ambiente. La mezcla de reacción fue pre-enfriada en un baño de hielo y se añadió la mezcla de hielo y solución acuosa 4N de HCl. La mezcla se agitó hasta que se disolvió todo el magnesio, las capas se separaron y la capa acuosa se

extrajo con éter dietílico (2x). Los materiales orgánicos combinados se lavaron con salmuera en neutralidad, se secaron sobre sulfato de sodio anhidro y se concentraron al vacío. El residuo se tomó para la siguiente etapa, en la cual fue hidrolizado en una mezcla a reflujo con MeOH (400 ml) y se añadió solución acuosa 3N de H_2SO_4 (100 ml) por 6 horas. La mezcla de reacción se enfrió, se concentró al vacío, se diluyó con agua helada y se extrajo con EtOAc (2x). Los materiales orgánicos combinados se lavaron con salmuera (2x), se secaron sobre sulfato de sodio anhidro y se concentraron al vacío. La cromatografía de columna (EtOAc/hexanos, 35/65) del residuo proporcionó la hidroxicetona deseada 64 (30 g).

^{1}H NMR ($CDCl_3$) δ 1.45 (br s, 1H), 1.59-1.63 (m, 2H), 1.73-1.83 (m, 4H), 1.93-1.97 (m, 2H), 2.20-2.28 (m, 2H), 2.65-2.76 (m, 4H), 7.19-7.24 (m, 3H), 7.28- 7.33 (m, 2H). Espectro de Masa (CI+) m/e =215.1 (M+1).

Etapa (D). En un matraz de fondo redondo de un solo cuello secado a la flama en un baño de hielo se colocó NaH (una dispersión al 60 % en aceite mineral) (1 equivalente, 0.66 g) y subsecuentemente se cargó con THF (20 ml) bajo una atmósfera de nitrógeno. A esta se añadió gota a gota fosfonoacetato de trimetilo (1 equivalente, 2.89 g/ 2.75 ml) vía jeringa. Cuando la evolución del hidrógeno pareció completa, se introdujo lentamente vía el embudo de adición

una solución de hidroxicetona 64 (15.5 mmoles, 3.33 g) en THF (40 ml). La mezcla de reacción se agitó a temperatura ambiente toda la noche. La reacción se detuvo con solución acuosa saturada de NH_4Cl seguido por agua y se extrajo con EtOAc (2x). Los materiales orgánicos combinados se lavaron con salmuera (2x), se secaron sobre sulfato de sodio anhidro y se concentraron al vacío. La cromatografía de columna del residuo (EtOAc/hexanos, 30/70) proporcionó el hidroxiacrilato deseado (3.5 g).

^1H NMR ($CDCl_3$) δ 1.16 (s, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.51-1.61 (m.4H), 1.70- 1.80 (m, 4H), 2.10-2.14 (m, 1H), 2.43-2.59 (m, 2H), 2.65 (t, J = 7.5 Hz, 2H), 3.46-3.50 (m, 1H), 4.16 (q, J = 7.1 Hz, 2H), 5.65 (s, 1H), 7.19-7.22 (m, 3H), 7.28-7.32 (m, 2H).

Etapa (E). El hidroxiacrilato (15.5 mmoles) obtenido anteriormente se hidrogenó sobre paladio (10 % sobre carbón) (10 % molar) en EtOAc (60 ml) usando gas hidrógeno a una presión atmosférica durante 10 horas. El Pd/C se separó por filtración a través de una capa de celita y el filtrado se concentró al vacío. El producto contuvo una mezcla de dos confórmeros (proporción de 3:1) del éster hidroxílico terciario deseado 65, el cual se separó por cromatografía de columna (EtOAc/hexanos, 20/80) y se caracterizó por los siguientes datos espectrales. En práctica, la mezcla conformérica se elaboró adicionalmente

sin separación.

^{1}H NMR (confórmero principal, $CDCl_3$) δ 1.06 (s,1H), 1.27(t, J=7.1 Hz, 3H), 1.33-1.42 (m, 4H), 1.46-1.51 (m,2H), 1.55- 1.66 (m, 4H), 1.68-1.76 (m, 3H), 2.23 (d, J = 7.0 Hz, 2H), 2.63 (t, J = 7.6 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 7.18-7.23 (m, 3H), 7.28-7.32 (m, 2H). Espectro de Masa (CI+) m/e = 287.1 (M+1);

^{1}H NMR (confórmero menor, $CDCl_3$) δ 1.07-1.15 (m, 2H), 1.22 (s, 1H), 1.27 (t, J=7.1 Hz, 3H), 1.39-1.44 (m, 2H), 1.54-1.58 (m, 2H), 1.67-1.75 (m, 6H), 1.88 (m, 1H), 2.22 (d, J=7.1 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 7.18-7.22 (m, 3H), 7.29-7.32 (m, 2H). Espectro de Masa (CI+) m/e = 287.1 (M+1).

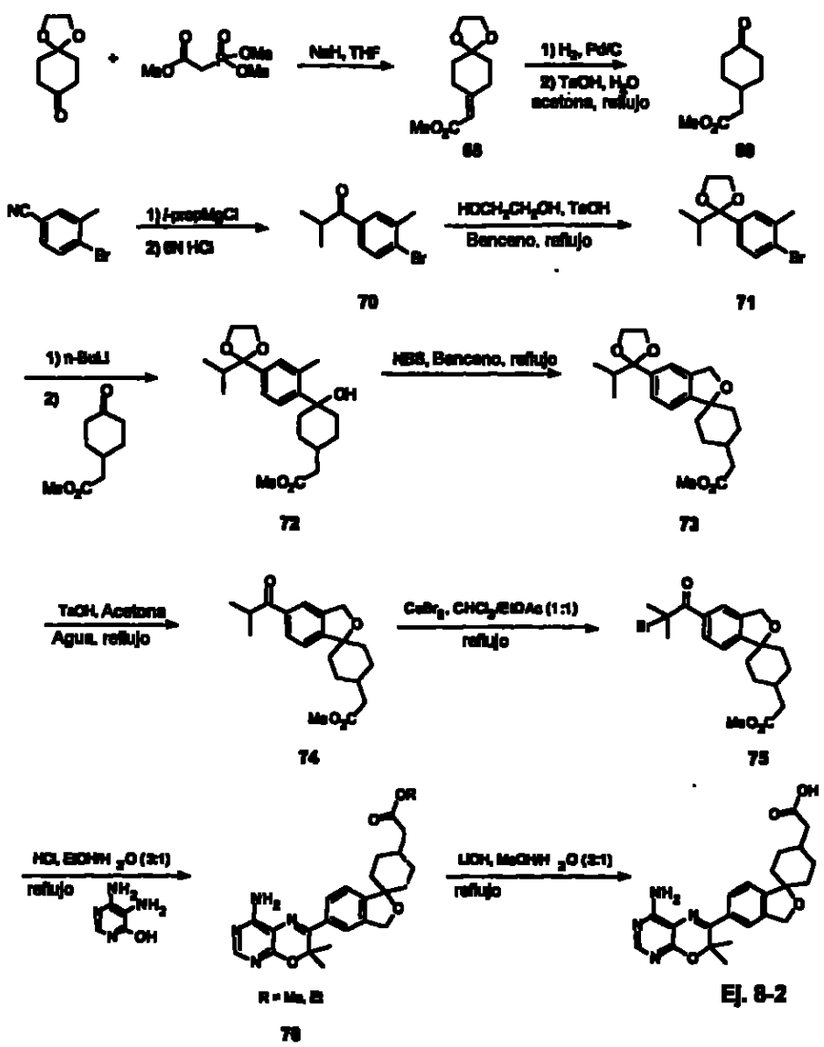
Etapas (F), (G) y (H). A un matraz de fondo redondo de un solo cuello de 50 ml secado a la flama en un baño salino de hielo se colocó $AlCl_3$ (2.5 equivalentes, 1.43 g) seguido por adición gota a gota de bromuro de 2-bromoisobutirilo (2 equivalentes, 2.01 g/1.08 ml) bajo una atmósfera de nitrógeno. La mezcla se agitó por aproximadamente 5 minutos, y se introdujo CH_2Cl_2 (8 ml). Después de otros 5 minutos, se añadió gota a gota una solución de CH_2Cl_2 (20 ml) de la mezcla conformérica de éster hidroxílico terciario 65 (4.3 mmoles, 1.23 g). La mezcla de reacción se agitó continuamente en el baño salino de hielo por 1 hora. Una mezcla de hielo y solución

acuosa de HCl 2N se añadió y la mezcla se agitó hasta que se disolvió todo y se extrajo con CH_2Cl_2 (2x). Los materiales orgánicos combinados se lavaron con salmuera (3x), se secaron sobre sulfato de sodio anhidro y se concentraron al vacío. El residuo contuvo principalmente dos regioisómeros de acilación en una proporción de aproximadamente 4 a 1, los cuales fueron ciclizados con hemisulfato de 4, 5-diamino- 6- hidroxipirimidina (0.5 equivalentes, 0.63 g) en la presencia de solución acuosa 2N de HCl (2.2 equivalentes, 4 ml) en EtOH-H_2O 3:1 (40 ml). La mezcla fue reflujada por aproximadamente 12 horas. La mezcla se enfrió, se diluyó con solución acuosa saturada de NH_4Cl y se extrajo con EtOAc (2x). Los materiales orgánicos combinados se lavaron con solución acuosa saturada de NH_4Cl (2x), se secaron sobre sulfato de sodio anhidro y se concentraron al vacío. El producto fue hidrolizado por medio de LiOH-H_2O (5 equivalentes, 0.73 g) en MeOH-H_2O 3:1 (20 ml). Usando el mismo procedimiento de elaboración usado en la etapa de ciclización precedente, se obtuvo una mezcla de dos regioisómeros principales (67). El isómero principal (1.2 g) se obtuvo por recristalización (EtOAc/CH_2Cl_2/MeOH). El isómero deseado (Ejemplo 8= (200 mg) se obtuvo por medio de HPLC preparatoria del licor madre.

^1H NMR ($CDCl_3$) (un confórmero único, *trans*-) δ 1.35-

1.43 (m, 2H), 1.69-1.88 (m, 16H), 1.96 (m, 1H), 2.36 (d, J=7.0 Hz, 2H), 2.83 (t, J=6.0 Hz, 2H), 7.34 (d, J = 1.6 Hz, 1H), 7.42 (dd, J = 8.4, 1.6 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 8.16 (s, 1H). Espectro de Masa (CI+) m/e = 435.2 (M+1).

Ejemplo 8-2



Compuesto 69. Se añadió fosfonoacetato de trimetilo (10.36 ml, 64.0 mmoles) a una suspensión de NaH en THF anhidro (500 ml) a 0 °C bajo una atmósfera de nitrógeno. Después de 30 minutos a 0 °C, se añadió vía cánula una solución de mono-etilen cetal 1, 4- ciclohexanodiona (10.0 g, 64.0 mmoles) en THF anhidro (50 ml). La mezcla de reacción se calentó a temperatura ambiente y se agitó por 12 horas. La reacción se detuvo con agua y se eliminó al vacío el THF. La capa acuosa se extrajo con EtOAc y se conjuntaron las capas orgánicas, se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron, y se concentraron al vacío para proporcionar 68 como un aceite incoloro. Se añadió Pd al 10 %/C a una solución de 68 en EtOH al 95 % (200 ml). La mezcla de reacción se agitó bajo una atmósfera de hidrógeno por 20 horas, se filtró a través de celita, y se concentró al vacío para proporcionar un aceite incoloro. Se añadió el ácido p-toluensulfónico monohidratado (1.21 g, 6.40 mmoles) a una solución del aceite en acetona (200 ml) y agua (50 ml) y la mezcla de reacción se calentó a reflujo por 24 horas. La acetona se eliminó al vacío y la solución acuosa se extrajo con EtOAc. Las capas orgánicas se conjuntaron, se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron, y se concentraron al vacío para proporcionar 69 como un líquido incoloro (5.86 g).

^{1}H NMR ($CDCl_3$) δ 1.46 (m, 2H), 2.08 (m, 2H), 2.25 - 2.33 (m, 3H), 2.37 (m, 4H), 3.68 (s, 3H). Espectro de Masa (ESI+) m/e = 171.1 (M+H).

Compuesto 70. Se añadió vía jeringa cloruro de isopropilmagnesio (25.5 ml, 51.0 mmoles) a una solución de 4- bromo- 3- metilbenzonitrilo (5.0 g, 25.5 mmoles) en Et_2O anhidro (50 ml) a 0 °C bajo una atmósfera de nitrógeno. La mezcla de reacción se calentó a reflujo por 12 horas. La mezcla de reacción se enfrió a 0 °C y se detuvo la reacción con HCl 6 N. Después de agitar a temperatura ambiente por 12 horas, se separaron las capas y la solución acuosa se extrajo con EtOAc. Se conjuntaron los extractos orgánicos, se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron, y se concentraron al vacío para proporcionar un aceite marrón. La cromatografía instantánea (ge de sílice, EtOAc al 2 %/hexanos) proporcionó un aceite incoloro (3.69 g).

^{1}H NMR (DMSO-d_6) δ 1.08 (d, J = 6.8 Hz, 6H), 2.41 (s, 3H), 3.62 (m, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.92 (s, 1H). Espectro de Masa (ESI+) m/e = 241.1 y 243.1 (M+H).

Compuesto 71. Se añadió ácido p-toluen sulfónico monohidratado (360 mg, 1.89 mmoles) a una solución de 70 (4.57 g, 18.9 mmoles) y etilen glicol (8.45 ml, 0.152 moles) en benceno (50 ml). La mezcla de reacción se

calentó a reflujo por 20 horas mientras se eliminó el agua usando una trampa de Dean-Stark. La solución se lavó con solución acuosa saturada de $NaHCO_3$, salmuera, se secó ($MgSO_4$), se filtró y se concentró al vacío para proporcionar un aceite incoloro. La cromatografía instantánea (gel de sílice, EtOAc al 2 %/hexanos) proporcionó 71 como un aceite incoloro (4.86 g).

^1H NMR (DMSO-d_6) δ 0.79 (d, J = 6.8 Hz, 6H), 2.03 (m, 1H), 2.34 (s, 3H), 3.63 (m, 2H), 3.92 (m, 2H), 7.07 (dd, J = 2.2 y 8.2 Hz, 1H), 7.30 (d, J = 2.1 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H). Espectro de Masa (ESI+) m/e = 285.0 y 287.1 (M+H).

Compuesto 72. Se añadió n-BuLi (5.4 ml, 13.5 mmoles) a una solución de 71 (3.50 g, 12.3 mmoles) en THF anhidro (20 ml) a - 78 °C. La solución se agitó a - 78 °C por 30 minutos y se añadió a una solución de 69 (2.30 g, 13.5 mmoles) en THF anhidro (20 ml) a - 78 °C. La mezcla de reacción se calentó a temperatura ambiente y se agitó por 12 horas. La reacción se detuvo con solución acuosa saturada de NH_4Cl y se separaron las capas. La capa acuosa se extrajo con EtOAc y los extractos orgánicos se conjuntaron, se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron al vacío para proporcionar un aceite amarillo. La cromatografía instantánea (gel de sílice, EtOAc al 15 %/hexanos) proporcionó 72 como un

aceite incoloro como una mezcla de los isómeros cis y trans (2.24 g).

^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 6.8 Hz, 6H), 0.88 (d, J = 6.8 Hz, 6H), 1.60-2.40 (m, 24H), 2.60 (s, 3H), 2.62 (s, 3H), 3.66 (s, 3H), 3.68 (s, 3H), 3.75 (m, 4H), 3.98 (m, 4H), 7.15-7.26 (m, 4H), 7.33 (m, 2H). Espectro de Masa (ESI+) m/e = 359.2 ([M-H_2O]+H).

Compuesto 73. Una solución de NBS (260 mg, 1.46 mmoles) y 72 (500 mg, 1.33 mmoles) en benceno (100 ml) se calentó a reflujo por 24 horas. La mezcla de reacción se enfrió a temperatura ambiente, se lavó con agua, salmuera, se secó ($MgSO_4$), se filtró y se concentró al vacío para proporcionar un aceite marrón. La cromatografía instantánea (gel de sílice, EtOAc al 10 %/ hexanos) proporcionó 73 como un aceite amarillo como una mezcla de los isómeros cis y trans (187 mg).

^{1}H NMR (DMSO-d_6) δ 0.88 (d, J = 6.8 Hz, 6H), 0.89 (d, J = 6.8 Hz, 6H), 1.54-2.10 (m, 20H) 2.28 (d, J = 7.0 Hz, 2H), 2.43 (d, J = 7.3 Hz, 2H), 3.68 (s, 3H), 3.70 (s, 3H), 3.76 (m, 4H), 3.97 (m, 4H), 5.02 (s, 2H), 5.03 (s, 2H), 7.00 (d, J = 7.8 Hz, 1H), 7.22 (m, 3H), 7.28 (m, 2H). Espectro de Masa (ESI+) m/e = 375.1 (M+H).

Compuesto 74. Una solución de 73 (450 mg, 1.20 mmoles) y ácido p-toluen sulfónico monohidratado (23.0 mg, 0.120 mmoles) en acetona (25 ml) y agua (5 ml) se calentó

a reflujo por 24 horas. Se eliminó la acetona al vacío y se extrajo la solución acuosa con EtOAc. Las capas orgánicas se conjuntaron, se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron al vacío para proporcionar un aceite amarillo como una mezcla de los isómeros cis y trans. (366 MG).

^1H NMR (DMSO-d_6) δ 1.09 (d, J = 6.8 Hz, 6H), 1.09 (d, J = 6.8 Hz, 6H), 1.40-1.83 (m, 18H) 2.25 (d, J = 7.0 Hz, 2H), 2.53 (d, J = 7.4 Hz, 2H), 3.59 (s, 3H), 3.60 (s, 3H), 3.63 (m, 2H), 4.98 (s, 4H), 7.38 (d, J = 7.9 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.87 (m, 4H). Espectro de Masa (ESI+) m/e = 331.2 (M+H).

Una mezcla de 74 (400 mg, 1.21 mmoles) y $CuBr_2$ (811 mg, 3.63 mmoles) en $CHCl_3$ (25 ml) y EtOAc (25 ml) se calentó a reflujo por 5 horas. Se eliminó el solvente al vacío y el residuo se dividió entre EtOAc y agua. Las capas se separaron y la solución acuosa se extrajo con EtOAc. Se conjuntaron las capas orgánicas, se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron al vacío para proporcionar 75 como un aceite amarillo. Se añadieron hemisulfato de 4, 5- diamino- 6-hidroxipirimidina (170 mg, 0.486 mmoles) y HCl 2N (535 µl, 1.07 mmoles) a una solución de 75 (398 mg, 0.972 mmoles) en EtOH (18 ml) y agua (6 ml). La mezcla de reacción se calentó a reflujo por 23 horas y se detuvo la reacción con

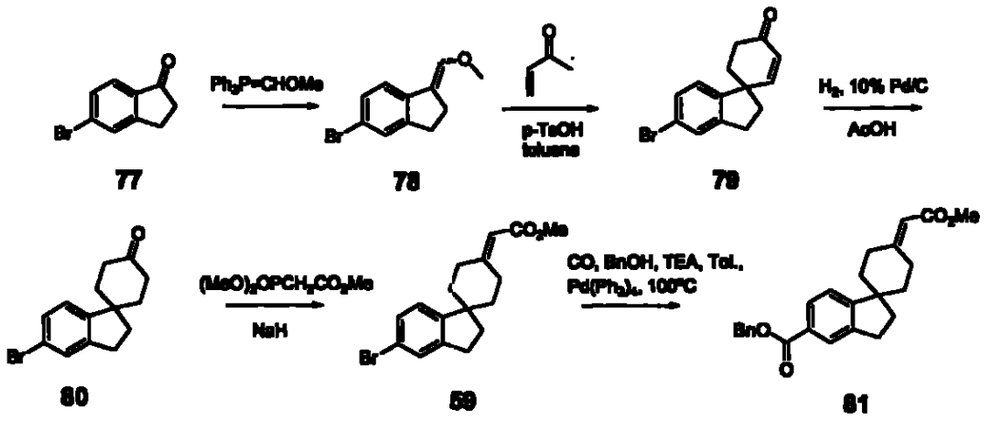
solución acuosa saturada de NH_4Cl. La solución se extrajo con EtOAc y las capas orgánicas se conjuntaron, se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron, y se concentraron al vacío para proporcionar 76 como una espuma naranja (360 mg). Se añadió hidróxido de litio monohidratado (173 mg, 4.12 mmoles) a una solución de 76 (360 mg, 0.825 mmoles) en MeOH (18 ml) y agua (6 ml). La mezcla de reacción se calentó a reflujo por 18 horas y se detuvo la reacción con NH_4Cl. La solución se acidificó con HCl y se extrajo con EtOAc. Se conjuntaron las capas orgánicas, se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron, y se concentraron al vacío para proporcionar el Ejemplo 8-2 como un sólido amarillo (145 mg), como una mezcla de los isómeros cis y trans, los cuales fueron separados por HPLC en fase inversa.

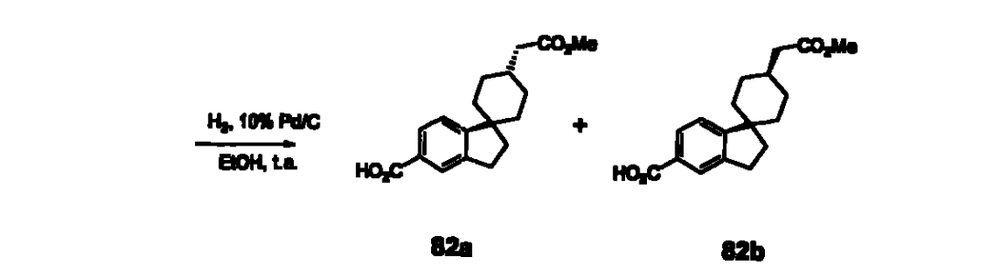
^1H NMR (isómero principal, DMSO-d_6) δ 1.50 (m, 5H), 1.61 (s,6H), 1.82 (m, 4H), 2.40 (d, J = 7.3 Hz, 2H), 4.97 (s, 2H), 7.53 (d, J = 7.9 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.62 (s, 1H), 7.99 (s, 1 H). Espectro de Masa (CI+) m/e = 423.2 (M + 1).

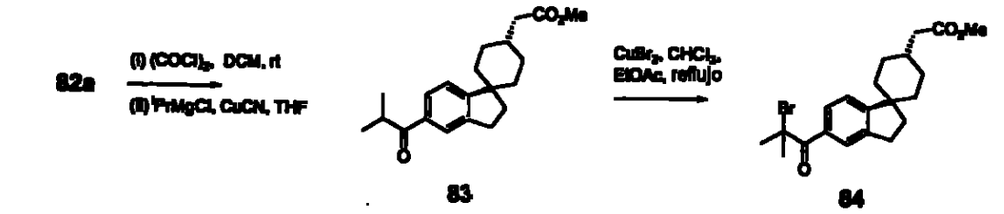
^1H NMR (isómero menor, DMSO-d_6) δ 1.40 (m, 2H), 1.60 (s, 6H), 1.64 (m, 4H), 1.75 (m, 3H), 2.15 (d, J = 6.9 Hz, 2H), 4.97 (s, 2H), 7.30 (d, J = 8.5 Hz, 1H), 7.61 (m, 2H), 7.98 (s, 1H). Espectro de Masa (CI+) m/e = 423.2 (M+1).

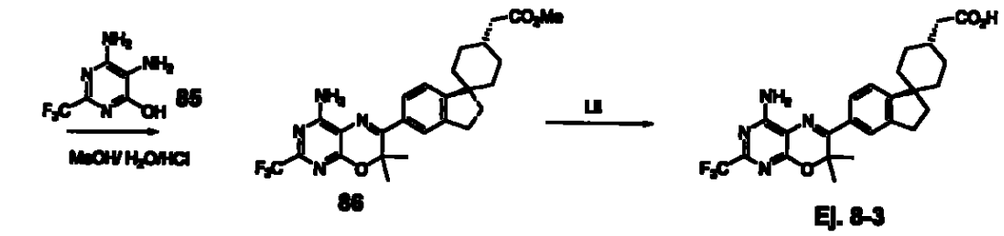
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Ejemplo 8-3:









Compuesto 78. a una suspensión agitada de terbutóxido de potasio (16.2 g, 142 mmoles) en 1, 4- dioxano (300 ml) se añadió cloruro de (metoximetil) trifenilfosfonio (48.5 g, 142 mmoles) a temperatura ambiente bajo N_2. Después de agitar por 2 horas, se añadió a la solución a temperatura ambiente bajo N_2, 5- bromoindanona (77, 13 g, 61.6 mmoles) en dioxano (170 ml). La mezcla se agitó por 2 horas a temperatura ambiente, se vertió en agua (500 ml) y se extrajo con EtOAc (500 ml). Se separaron las capas orgánicas , se lavaron con salmuera, se secaron sobre Na_2SO_4, y se concentraron al vacío. Al residuo se añadió hexano:EtOAc (2:1 (500 ml)). La mezcla se agitó a temperatura ambiente, se filtró y el precipitado se lavó con 2x hexano:EtOAc (2:1 (500 ml)). El filtrado se concentró al vacío y el residuo se destiló (700 mm Torr a 145-150 °C) para dar el Compuesto 78 como un sólido amarillo claro de la mezcla cis y trans (14.5 g).

^1H NMR ($CDCl_3$) δ 2.70-2.80 (m, 2H, isómeros principales y menores), 2.94 - 3.00 (m, 2H, isómeros principales y menores), 3.75 (s, 3H, isómeros principales y menores), 6.20 (t, J = 1.8 Hz, 1H, solamente isómeros menores), 6.65 (t, J = 2.6 Hz, 1H, isómero principal solamente), 7.12 (d, J = 8.2 Hz, 1H, solamente isómero principal), 7.22-7.34 (m, 2H, isómeros principales y menores), 7.68 (d, J= 8.2 Hz, 1H, isómero menor

solamente).

Compuesto 79. A una solución agitada de 78 (14.5 g, 60.8 mmoles) en tolueno (60 ml) se añadió metilvinil cetona (6.0 ml, 68 mmoles) y ácido p-toluensulfónico monohidratado (1.2 g, 6.3 mmoles) a t.a. La mezcla se calentó a 100 °C por 18 horas bajo N_2, se dejó enfriar a t.a. y se vertió en solución acuosa saturada de $NaHCO_3$ (200 ml). La capa orgánica se separó y se lavó con salmuera. La capa acuosa se extrajo con EtOAc y la capa orgánica se separó y se lavó con salmuera. La capa orgánica se secó sobre Na_2SO_4 y se concentró al vacío. El residuo se recristalizó a partir de EtOH-H_2O (2:1 (168 ml)), se filtró y se secó al vacío a 60 °C para dar 79 como un sólido amarillo pálido (9.90 g).

^1H NMR ($CDCl_3$) δ 2.09-2.24 (m, 3H), 2.29-2.32 (m, 1H), 2.54 (dd, J = 7.2,6.3 Hz, 2H), 2.99- 3.12 (m, 2H), 6.10 (d, J = 10.1 Hz, 1H), 6.76 (d, J = 10.1 Hz, 1H), 6.99 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.44 (s, 1H).

Compuesto 80. A una solución agitada de 79 (153.4 g, 0.55 M) en ácido acético (3.7 l) se añadió PD al 10 %/C (30 g). La mezcla se agitó bajo una atmósfera de hidrógeno por 4 horas y se filtró a través de gel de sílice (lavando con ácido acético seguido por DCM). El filtrado se concentró al vacío para producir 80 como un sólido blanco (150.51 g).

^{1}H NMR ($CDCl_3$) δ 1.90- 1.97 (m, 2H), 2.02-2.12 (m, 2H), 2.26 (t, J = 7.3 Hz, 2H), 2.43-2.61 (m, 4H), 3.01 (t, J = 7.3 Hz, 2H), 7.04 (d, J = 8.1 Hz, 1H), 7.32-7.35 (m, 1H), 7.40 (s, 1H).

Compuesto 59. A una solución agitada de fosfonoacetato de trimetilo (116.45 g, 640 mmoles) en THF anhidro (2.2 l) bajo una atmósfera de N_2 a 0 °C se añadió por porciones durante 7 minutos hidruro de sodio (25.6 g de dispersión al 60 % en aceite mineral, 640 mmoles). La mezcla se agitó a 0 °C por 30 minutos y se dejó calentar a t.a. durante 30 minutos. Una solución de 80 (149 g, 533 mmoles) en THF anhidro (375 ml) se añadió durante 10 minutos. La mezcla se agitó a t.a. por 90 minutos y se añadió solución acuosa saturada de NH_4Cl (500 ml). La mezcla se agitó por 5 minutos y se concentró al vacío para eliminar el THF. La fase acuosa se lavó con éter dietílico (1 l y 500 ml). Las fracciones orgánicas combinadas se lavaron con solución de salmuera, se secó ($MgSO_4$) y se concentró al vacío. La trituración del residuo oleoso resultante produjo un sólido blanco, el cual se colectó por filtración y se lavó con hexano para dar 59 (62.0 g). El licor madre se concentró al vacío y el residuo se recristalizó a partir de EtOAc/hexano a 0 °c para producir 59 adicional (38.3 g). Unas tres iteracciones adicionales del método de recristalización anterior produjo 59

adicional (40.5 g)

^{1}H NMR ($CDCl_3$) δ 1.68-1.78 (m, 4H), 2.11-2.21 (m, 3H), 2.31-2.46 (m, 2H), 2.95 (t, J = 7.4 Hz, 2H), 3.73 (s, 3H), 3.82-3.87 (m, 2H), 5.73 (s, 1H), 6.99 (d, J = 8.0 Hz, 2H). 7.29- 7.32 (m, 1H), 7.37 (s, 1H).

Compuesto 82a. A un matraz de fondo redondo de tres cuellos de 5 litros que contenía 59 (140 g, 418 mmoles) se añadió Et_3N (280 ml, 2.03 moles), alcohol bencílico (420 ml, 4.06 mmoles) y tolueno (1.4 l). La solución que resultó se purgó con CO por 5 minutos antes de adición de $Pd(PPh_3)_4$ (9.34 g, 8 mmoles). La reacción se calentó a 90 °C por 8 horas con purga de CO. La mezcla se agitó en un baño de hielo por 30 minutos y se filtró, y el precipitado se lavó con EtOAc. El filtrado se lavó con agua, salmuera y se secó sobre sulfato de sodio. Los solventes y el exceso de alcohol bencílico se eliminaron al vacío. El residuo se disolvió en DCM (50 ml) y hexano (50 ml) y se filtró a través de un embudo lleno con gel de sílice (500 g). El gel de sílice impregnado se lavó con hexano/EtOAc (gradiente de elución: 9/1 a 1/1. La concentración al vacío produjo 81 como aceite amarillo (160 g). El Compuesto 81 se disolvió en EtOH (12 l) y se añadió Pd sobre carbón (10 %, 20 g). La mezcla se agitó bajo una atmósfera de hidrógeno por 2 días, se filtró a través de una capa de celita y se concentró al vacío para dar un

sólido blanco (120 g) al producto crudo se añadió EtOAc (200 ml) y la mezcla se calentó a reflujo por 1 minuto, y se filtró. El filtrado se recalentó a reflujo y se añadió hexano lentamente. La mezcla resultante se enfrió lentamente a t.a. para producir un sólido cristalino blanco, el cual se colectó por filtración (44 g del isómero trans 82a). El licor madre se concentró y la recristalización a partir de EtOAc:hexano produjo unos 16 g adicionales de 82a.

^{1}H NMR ($CDCl_3$) δ 1.23-1.27 (m, 2H), 1.59-1.90 (m, 7H), 2.03 (t, J = 7.4 Hz, 2H), 2.28 (d, J = 7.0 Hz, 2H), 2.93 (t, J = 7.4 Hz, 2H), 3.70 (s, 3H), 7.21 (d, J = 7.9 Hz, 1H), 7.93 (s, 1H), 7.95 (d, J = 7.9 Hz, 1H). Espectro de Masa (ESI+) m/e = 303 (M+1).

Compuesto 83. Se añadió DMF (200 µl) a una solución de 82a (57.23 g, 0.189 moles) y cloruro de oxalilo (19.8 ml, 0.227 moles) en CH_2Cl_2 (500 ml) a 0 °C bajo una atmósfera de nitrógeno. La mezcla de reacción se agitó a 0 °C por 15 minutos y a t.a. por 3 horas. Se eliminó el solvente al vacío para proporcionar el cloruro ácido como un sólido blancuzco (60.3 g). Un matraz de fondo redondo de tres cuellos de 2 litros se cargó con CuCN (4.19 g, 46.8 mmoles) y THF anhidro (500 ml) y se enfrió a - 25 °C. A esta suspensión agitada se añadió gota a gota una solución 2M de cloruro de isopropilmagnesio (46.8 ml, 93.5

mmoles en THF) mientras que se mantenía una temperatura interna de entre -25 °C y -22 °C. A esta solución se añadió gota a gota una solución del cloruro ácido (preparación descrita anteriormente) (10 g, 31.2 mmoles) en THF anhidro (50 ml) mientras se mantenía a temperatura interna d entre -20 y -17 °C. La mezcla de reacción se agitó a - 15 °C por 1 hora y se detuvo la reacción con NH_4OH al 10 % en solución acuosa saturada de NH_4Cl (300 ml). Esta solución se calentó a t.a. y las capas se separaron. La capa orgánica se lavó con NH_4OH al 10 % en solución acuosa saturada de NH_4Cl (2 x 300 ml), salmuera (1 x 300 ml), se secó ($MgSO_4$), se filtró, y se concentró al vacío para proporcionar 83 como un sólido blancuzco (10.08 g).

^1H NMR ($CDCl_3$) δ 7.83 (m, 2H), 7.22 (d, J = 8.4 Hz, 1H), 3.72 (s, 3H), 3.54-3.58 (m, 1H), 2.94 (t, J = 7.4 Hz, 2H), 2.30 (d, J = 7.0 Hz, 2H), 2.04 (t, J = 7.4 Hz, 2H), 1.92 (m, 1H), 1.78 (m, 2H), 1.69-1.64 (m, 4H), 1.28 (m, 2H), 1.23(d, J = 6.8 Hz, 6H). Espectro de Masa (ESI+) m/e = 329 (M+1).

Compuesto 84. Una solución de 83 (5 g, 15.2 mmoles) en EtOAc (100 ml) y cloroformo (100 ml) se trató con $CuBr_2$ (10 g, 44.8 mmoles) y la mezcla se calentó a reflujo por 8 horas antes de ser enfriada a t.a. La mezcla de reacción se filtró y se lavó con EtOAc. El filtrado se lavó con agua, salmuera y se secó sobre sulfato de sodio. Los

solventes se eliminaron entonces al vacío y se añadió hexano. Se formó un sólido blanco 84 con agitación y se colectó por filtración (5 g). Se obtuvo 84 (0.76 g) adicional por recristalización a partir del licor madre a 0 °C.

^{1}H NMR ($CDCl_3$) δ 1.25-1.28 (m, 2H), 1.61- 1.92 (m, 7H), 2.03-2.06 (m, 8H), 2.29 (d, J = 7.0 Hz, 2H), 2.94 (t, J = 7.4 Hz, 2H), 3.72 (s, 3H), 7.19 (d, J = 8.0 Hz, 1H), 7.99 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H). Espectro de Masa (ESI+) m/e = 407 y 409 (M+1).

Compuesto 86. A 84 (0.5 g, 1.23 mmoles) y 4, 5-diamino- 6- hidroxi- 2- trifluorometilpirimidina (85, J. A. Barone y colaboradores, J. Med. Chem., 1969, 6, 39; P. D. Landauer y colaboradores, J. Chem. Soc., 1953, 3721.) (0.26 g, 1.34 mmoles) se añadió metanol (13 ml), HCl 2N (2 ml) y agua (5 ml). La mezcla se calentó a reflujo por 24 horas, se enfrió y se concentró al vacío. Al residuo se añadió agua (10 ml) y el precipitado resultante se colectó por filtración, se lavó con pentano y se secó al vacío para producir 86 (375 mg) como un sólido blanco.

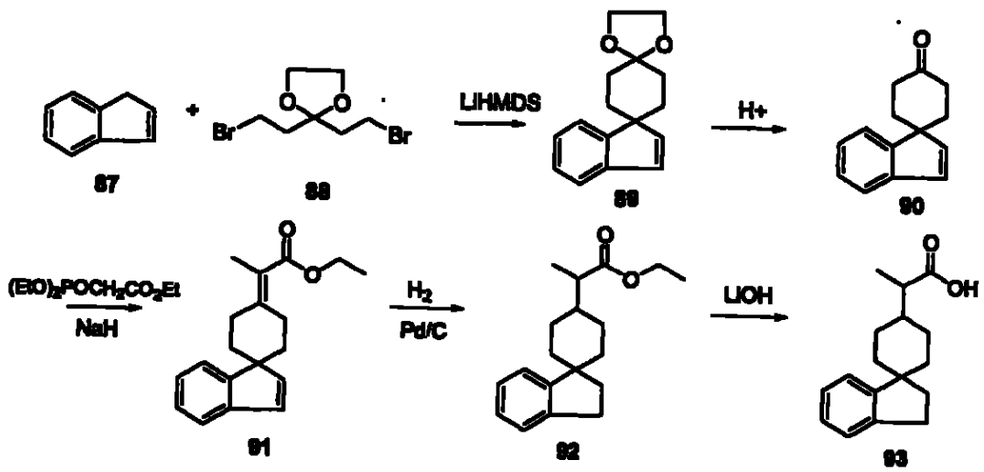
^{1}H NMR (DMSO-d_6) δ 1.18-1.27 (m, 2H), 1.48-1.86 (m, 13H), 1.98 (t, J = 7.3 Hz, 2H), 2.28 (d, J = 7.2 Hz, 2H), 2.89 (t, J = 7.1 Hz, 2H), 3.61 (s, 3H), 7.28 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.58 (s, 1H).

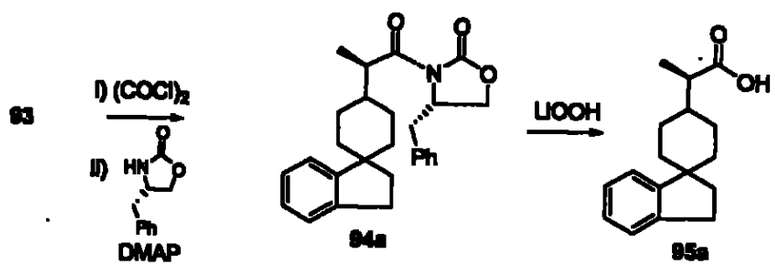
Ejemplo 8-3. A una solución agitada de 86 (100 mg,

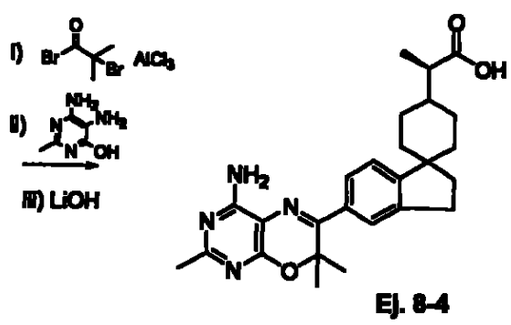
0.199 mmoles) en DMF (1 ml) se añadió ioduro de litio anhidro (670 mg, 5 mmoles). La mezcla se calentó a 125-130 °C por 24 horas y se vertió en agua (20 ml). el precipitado resultante se colectó por filtración y se lavó con agua. El precipitado se recristalizó a partir de etanol para producir el Ejemplo 8-3 (70 mg) como un sólido blanco.

^{1}H NMR (DMSO-d_6) δ 1.17-1.26 (m, 2H), 1.48-1.82 (m, 16H), 1.98 (t, J= 7.4 Hz, 2H), 2.18 (d, J = 6.8 Hz, 2H), 2.90 (t, J = 7.2 Hz, 2H), 7.28 (d, J = 8.1 Hz, 1H), 7.37 (brs, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.58 (s, 1H), 7.80 (brs, 1H), 12.05 (brs, 1H).

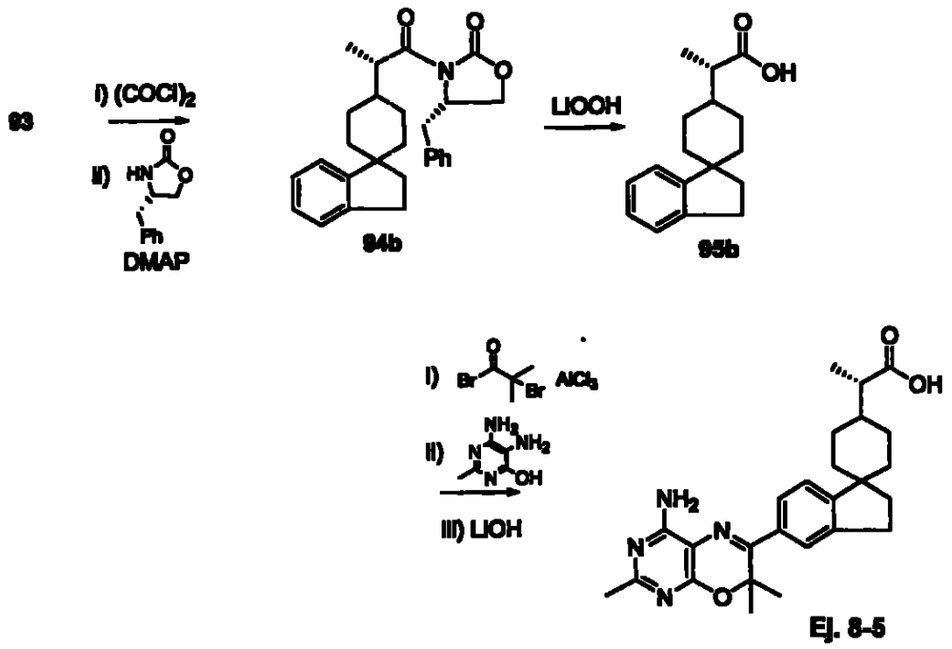
Ejemplo 8-4:







Ej. 8-4



Ej. 8-5

Compuesto 89. Un matraz de fondo redondo de un solo cuello de 500 ml seco se cargó con indeno 87 (8.91 g, 76.65 mmoles) y THF (60 ml). La solución se agitó y se enfrió en un baño de hielo. Al matraz se añadió litio bis(trimetilsilil)amida (153.3 ml, 1.0 M en THF, 153.3 mmoles) a través de una jeringa durante un período de 30 minutos. La mezcla resultante se agitó a 0 °C por 30 minutos, y se transfirió por medio de una cánula a una solución agitada del dibromocetal 88 (20.0 g, 66.23 mmoles) en THF a 0 °C durante 30 minutos. Después de adición, la mezcla de reacción se agitó por 2 horas a 0 °C y 30 minutos a t.a. El solvente se evaporó al vacío y el residuo se purificó por cromatografía sobre gel de sílice

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(hexano/EtOAc 25/1 a 15/1; elución con gradiente) para dar el Compuesto 89 (15.0 g) como cristales amarillo claro.

^{1}H NMR ($CDCl_3$) δ 1.43 (d, J = 13.5 Hz, 2H), 1.88-1.99 (m, 4H), 2.20 (d, J = 4.0, 13.0 Hz, 2H), 4.06 (s, 4H), 6.78 (d, J = 6.0, 1H), 6.85 (d, J = 6.0, 1H), 7.20-7.27 (m, 2H), 7.34 (d, J = 7.5, 1H), 7.42 (d, J = 7.5, 1H). Espectro de Masa (ESI+) m/e = 243 (M++1).

Compuesto 90. a una solución de 89 (15.0 g, 62 mmoles) en MeOH (350 ml) se añadió H_2SO_4 3M (60 ml). La mezcla de reacción se calentó a reflujo por 7 horas bajo una atmósfera de nitrógeno. La mezcla se enfrió a t.a. y el MeOH se eliminó al vacío. La mezcla se diluyó con agua helada y se extrajo con EtOAc (100 ml x 3), se lavó con agua (25 ml x 2) y salmuera (20 ml) y se secó sobre MgSO4. La concentración al vacío dio un producto crudo, el cual fue purificado por cromatografía de columna sobre gel de sílice (hexano/EtOAc 20/1) para dar el Compuesto 90 (10.0 g) como un sólido blanco.

^{1}H NMR ($CDCl_3$) δ 1.76 (m, 2H), 2.34 (m, 2H), 2.68 (m, 4H), 6.90 (d, J = 6.0, 1H), 6.95 (d, J = 6.0, 1H), 7.25-7.51 (m, 4H). Espectro de Masa (ESI+) m/e = 199 (M+1)

Compuesto 91. Una suspensión de NaH (dispersión al 60 % en aceite mineral) (2.45 g, 61.25 mmoles) en THF (200 ml) en un matraz de 500 ml previamente secado, se enfrió a 0 °C bajo una atmósfera de nitrógeno. Al matraz se añadió

gota a gota una solución de 2-fosfonopropionato de trietilo (14.6 g, 61.25 mmoles) en THF (10 ml)a 0 °C durante 15 minutos. La mezcla fue agitada a 0 °C por 15 minutos y se añadió gota agota a través de un embudo adicional durante 25 minutos una solución de 90 (7.8 g, 39.20 mmoles) en THF (50 ml). después de adición, la mezcla se agitó a t.a. toda la noche. La reacción se detuvo con solución acuosa saturada de NH4Cl y se extrajo con EtOAc, se lavó con agua y salmuera, y se secó sobre MgSO4. La evaporación del solvente dio un producto crudo, el cual fue purificado por cromatografía de columna sobre gel de sílice (hexano/EtOAc 20/1) para dar el Compuesto 91 (10.0 g) como un sólido blanco.

^{1}H NMR (CDCl3) δ 1.35 (t, J = 7.1 Hz, 3H), 1.5-1.60 (m, 2H), 1.98 (5, 3H), 1.95-2.05 (m, 2H), 2.25-2.48 (m, 2H), 2.75-2.90 (m, 1H), 3.10-3.25 (m, 1H), 4.25 (q, J = 7.1 Hz, 2H), 6.81 (d, J = 5.7, 1H), 6.93 (d, J = 5.7, 1H), 7.20-7.36 (m, 4H).

Compuesto 92. Se disolvió 91 (5.6 g, 19.72 mmoles) en EtOAc (60 ml) y se hidrogenó sobre paladio (10 % sobre carbón) usando gas hidrógeno a una presión atmosférica por 24 horas. La mezcla se filtró a través de celita y el filtrado se concentró al vacío para dar el producto 92 (5.4 g) como aceite incoloro, el cual se usó directamente en la siguiente reacción sin purificación adicional.

^{1}H NMR ($CDCl_3$) δ 1.18 (d, J = 7.0 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.61-1.85 (m, 9H), 1.98 (t, J = 7.5 Hz, 2H), 2.31 (m, 1H), 2.89 (t, J = 7.4 Hz, 2H), 4.14-4.19 (m, 2H), 7.05-7.20 (m, 4H).

Compuesto 93. Se disolvió 92 (2.63 g, 9.21 mmoles) en MeOH/THF/H_2O (40 ml, 5/2/1). A la solución anterior se añadió hidróxido de litio monohidratado (1.93 g, 46.0 mmoles) y la mezcla se agitó a 50 °C toda la noche. Se eliminó el MeOH al vacío y la mezcla de reacción se acidificó con HCl 2N. La mezcla se extrajo con EtOAc (25 ml x 3), se lavó con agua, salmuera y se secó sobre $MgSO_4$. La evaporación del solvente dio un producto crudo que fue purificado por cromatografía de columna sobre gel de sílice (hexano/EtOAc, 8/1) para dar el Compuesto 93 (2.38 g) como un sólido blanco.

^{1}H NMR ($CDCl_3$) δ 1.24 (d, J = 7.02 Hz, 3H), 1.61-1.85 (m, 10H), 1.95-2.0 (m, 2H), 2.3-2.4 (m, 1H), 2.88-2.92 (m, 2H), 7.05-7.20 (m, 4H). Espectro de Masa (ESI+) m/e = 258 (M).

Compuesto 94a y 94b. A 93 (2.2 g, 8.53 mmoles) en CH_2Cl_2 a 0 °C bajo una atmósfera de nitrógeno se añadió $(COCl)_2$ (0.82 ml, 9.38 mmoles) y una gota de DMF. La reacción se agitó a 0 °C por 1 hora. A esta solución de cloruro ácido generado se añadió una solución de (S)-(-)-4-bencil- 2- oxazolidona (1.66 g, 9.37 mmoles), DMAP (1.09

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g, 8.92 mmoles) y trietilamina (1.88 ml, 13.49 mmoles(en CH2Cl2 gota a gota a 0 °C bajo una atmósfera de nitrógeno. Después de adición, la mezcla se agitó a t.a. por 2 horas. La reacción se detuvo por adición de solución acuosa saturada de NH4Cl, se extrajo con EtOAc (25 ml x 3), se lavó con agua (10 ml x 2), salmuera y se secó sobre MgSO4. La concentración al vacío dio un producto crudo, el cual fue purificado por cromatografía de columna sobre gel de sílice (hexano/EtOAc 19/1 a 10/1) para dar el Compuesto 94a (926 mg) y 94b (1.27 g). Nota: la asignación estereoquímica de 94a y 94b es arbitraria.

Compuesto 94a: ^{1}H NMR ($CDCl_3$) δ 1.26 (d, J = 6.9 Hz, 3H), 1.61-1.80 (m, 2H), 1.80-1.95 (m, 7H), 1.99 (t, J = 7.3 Hz, 2H), 2.80 (dd, J -9.6, J = 13.3 Hz, 1H), 2.91 (t, J = 7.4 Hz, 2H), 3.33 (dd, J -3.2, 13.3 Hz, 1H), 3.71-3.75 (m, 1H), 4.15-4.23 (m, 2H), 4.70- 4.78 (m, 1H), 7.05-7.37 (m, 9H). Espectro de Masa (ESI+) m/e = 418 (M+1). $[\alpha]^{26}$ = +54.85 (c = 0.60, CH_2Cl_2).

Compuesto 94b: ^{1}H NMR ($CDCl_3$) δ 1.21 (d, J = 6.9 Hz, 3H), 1.25-1.95 (m, 9H), 2.01 (t, J = 7.4 Hz, 2H), 2.75 (m, 1H), 2.90 (t, J = 7.3 Hz, 2H), 3.32-3.41 (m, 1H), 3.73-3.78 (m, 1H), 4.12-4.22 (m, 2H), 4.73-4.77 (m, 1H), 7.05-7.39 (m, 9H). Espectro de Masa (ESI+) m/e = 418 (M+1). $[\alpha]^{26}$ = +10.12 (c = 0.60, CH_2Cl_2).

Compuesto 95a. A una solución agitada de 94a (900 mg,

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2.16 mmoles) en THF (30 ml) y H_2O (10 ml) se añadió H_2O_2 (30 %, 1.8 ml, 17.7 mmoles) e hidróxido de litio monohidratado (360 mg, 8.55 mmoles) a 0 °C. La reacción se dejó calentar a t.a. toda la noche y se detuvo la reacción con solución acuosa saturada de Na_2SO_3 y se acidificó con HCl al 10 %. La mezcla se extrajo con EtOAc (15 ml x 3), se lavó con agua (5 ml x 2), salmuera y se secó sobre MgSO4. La concentración al vacío dio un producto crudo, el cual fue purificado por cromatografía de columna sobre gel de sílice (hexano/EtOAc, 8/1) para dar el Compuesto 95a (500 mg) como un sólido blanco.

^1H NMR ($CDCl_3$) δ 1.24 (d, J = 7.0 Hz, 3H), 1.61-1.85 (m, 10H), 1.95-2.0 (m, 2H), 2.30-2.40 (m, 1H), 2.88-2.92 (m. 2H), 7.05- 7.20 (m, 4H). Espectro de Masa (ESI+) m/e = 258.

Compuesto 95b. El Compuesto 95b (ent-95a) se preparó a partir de 94b de una manera similar a la descrita para la conversión de 94a a 95a anteriores.

Ejemplo 8-4. A una suspensión de $AlCl_3$ anhidro (484 mg, 3.63 mmoles) en CH_2Cl_2 (5 ml) se añadió gota a gota a 0 °C bromuro de 2- bromoisobutirilo (0.21 ml, 1.70 mmoles) bajo una atmósfera de nitrógeno. Después de que la mezcla se agitó por 5 minutos, se añadió gota a gota una solución de Compuesto 95a (376 mg, 1.46 mmoles) en CH_2Cl_2 (20 ml). Después de agitar a 0 °C por una hora, la mezcla

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se vertió en agua helada y se extrajo con CH_2Cl_2 (15 ml x 3). La capa orgánica combinada se lavó sucesivamente con agua, solución saturada de $NaHCO_3$ y salmuera, se secó sobre MgSO4 y se concentró al vacío. Al residuo se añadió 2-metil-4,5-diamino-6-hidroxipirimidina (PD Landauer y colaboradores, J. Chem. Soc., 1953, 3721) (250 mg, 1.54 mmoles), HCl 1N (5 ml, 5 mmoles), agua (5 ml) y EtOH (25 ml). La mezcla de reacción se calentó a reflujo toda la noche. La mezcla de reacción se enfrió a t.a. y se eliminó el EtOH por evaporación. El residuo se diluyó con solución acuosa saturada de NH4Cl y se extrajo con EtOAc (15 ml x 3). La capa orgánica combinada se lavó sucesivamente con agua y salmuera, se secó sobre $MgSO_4$ y se concentró al vacío. Al residuo se añadió MeOH/THF/H_2O (15 ml, 1/1/1) e hidróxido de litio monohidratado (200 mg, 4.77 mmoles) y la mezcla se agitó a 45 °C por 40 horas. Se eliminó el MeOH al vacío y el residuo se acidificó con HCl 2N. Esta mezcla se extrajo con EtOAc (15 ml x 3), se lavó con agua, salmuera y se secó sobre $MgSO_4$. La concentración al vacío dio un producto crudo, el cual fue purificado por HPLC (en fase inversa) para dar el Compuesto del Ej. 8-4 (65.6 mg) como un sólido blanco.

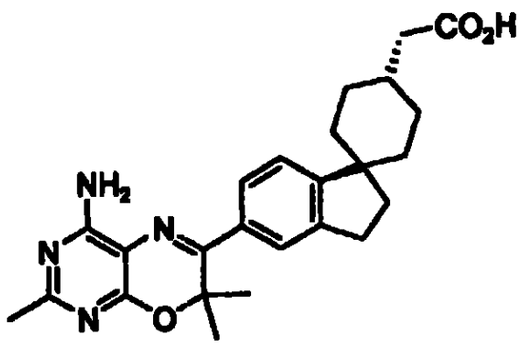
^1H NMR (DMSO-d_6) δ 1.07 (d, J = 7.0 Hz, 3H), 1.15-1.35 (m, 1H), 1.50-1.81 (m, 6H), 1.63 (s, 6H), 1.96 (t, J = 7.5 Hz, 2H), 2.21 (m, 1H), 2.34 (s, 3H), 2.45-2.55 (m, 2H),

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2.88 (t, J = 7.5, 2H), 7.25 (m, 1H), 7.51-7.54 (m, 4H), 12.0 (bs, 1H). Espectro de Masa (ESI+) m/e = 449 (M+1).

Ejemplo 8-5. El Compuesto Ej. 8-5 (ent-Ej.8-4) se preparó de una manera similar a la preparación del Ej. 8-4 a partir de 95a anterior.

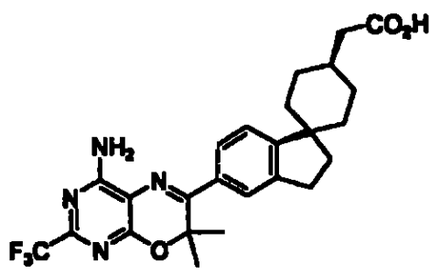
Ejemplo 8-6:



Este compuesto se obtuvo de la misma manera que en el Ejemplo 8.

^{1}H NMR (DMSO-d_6) δ 1.14-1.23 (m, 2H), 1.47-1.80 (m, 15H), 1.96 (t, J = 7.3 Hz, 2H), 2.15 (d, J = 7.0 Hz, 2H), 2.32 (s, 3H), 2.87 (t, J = 7.3 Hz, 2H), 7.10 (s, br, 2H), 7.24 (d, J = 7.8 Hz, 1H), 7.43- 7.50 (m. 2H).

Ejemplo 8-7:



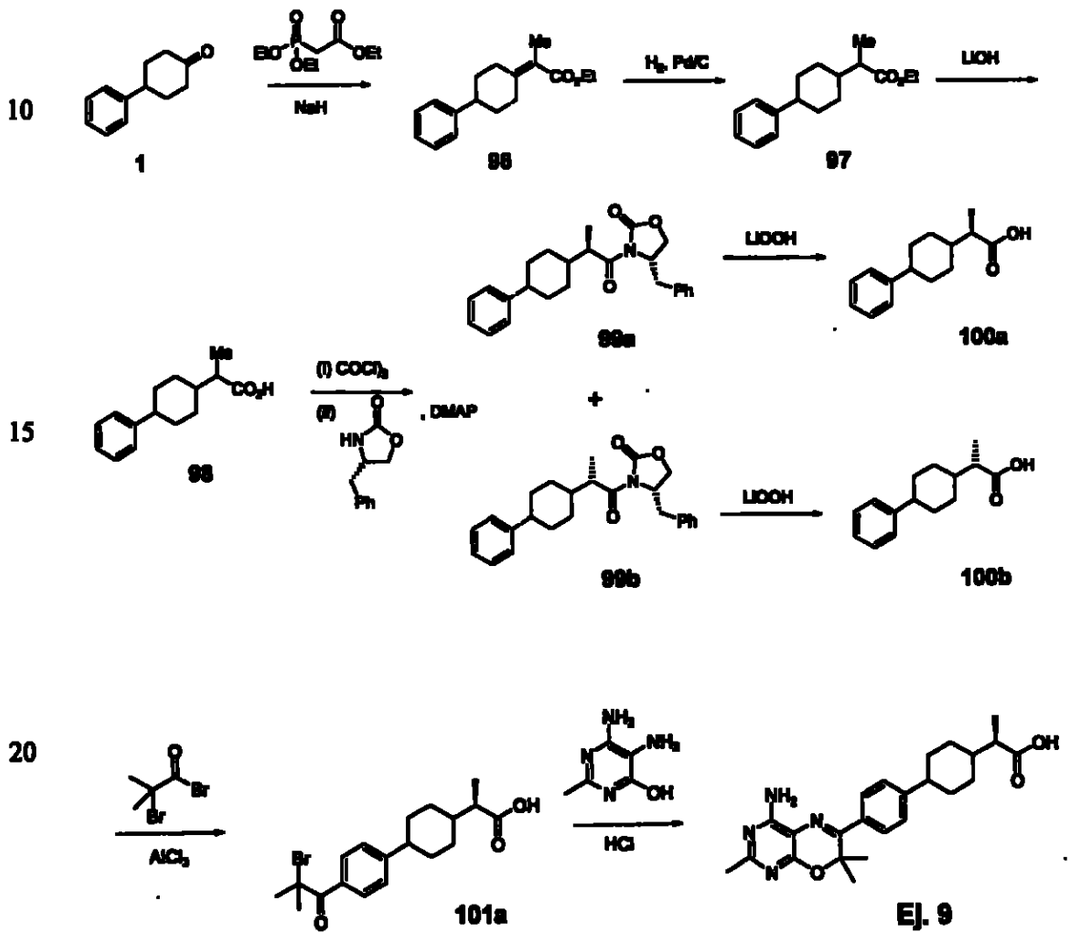
Este compuesto se obtuvo de la misma manera que en el

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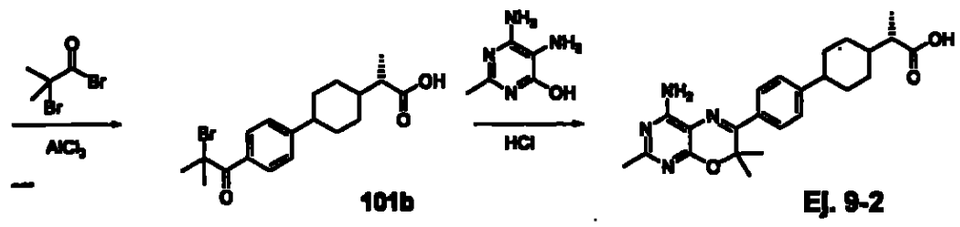
Ejemplo 8.

^{1}H NMR (DMSO-d_6) δ 1.39-1.45 (m, 2H), 1.47.1.55 (m, 2H), 1.60-1.75 (m, 10H), 1.94 (t, J = 7.2 Hz, 2H), 2.03 (m, 1H), 2.38 (d, J = 7.3 Hz, 2H), 2.87 (t, J = 7.3 Hz, 2H), 7.35 (s, br, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.57 (s, 1H), 7.77 (s, br, 1H).

Ejemplo 9



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Compuesto 97. Se preparó el Compuesto 96 a partir de 4-fenilciclohexanona y fosfonopropionato de trietilo de una manera similar a la descrita para la conversión de 1 a 2 (Ejemplo 2). El Compuesto 97 se preparó a partir de 96 de una manera similar a la descrita para la conversión de 2 a 3 (Ejemplo 2).

Compuesto 98. A una solución agitada de 97 (2.86 g, 11 mmoles) en metanol (83 ml) se añadió hidróxido de litio (2.62 g, 110 mmoles) en agua (28 ml). La mezcla se calentó a reflujo por 2 horas y se dejó enfriar a t.a., y se eliminó el metanol al vacío. La solución acuosa se lavó con éter dietílico, se acidificó a pH de 1 con HCl 1N y se extrajo con éter dietílico (3x). Los materiales orgánicos combinados se secaron (MgSO4), se filtraron y se concentraron al vacío para producir 98 (2.31 g) como un sólido blanco.

^{1}H NMR ($CDCl_3$) δ 1.23 (d, J = 7.2 Hz, 3H), 1.29-1.33 (m, 2H), 1.42-1.59 (m, 2H), 1.69-1.80 (m, 2H), 1.85-2.00 (m, 3H), 2.30-2.39 (m, 1H), 2.45-2.60 (m, 1H), 7.21-7.34

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(m, 5H).

Compuestos 99a y 99b. A una solución agitada de 98 (13.5 g, 58.1 mmoles) en DCM (225 ml) se añadieron 3 gotas de DMF. La mezcla se enfrió a 0 °C y se añadió gota a gota cloruro de oxalilo (5.58 ml, 63.91 mmoles). La mezcla se agitó a t.a. por 2 horas y se añadió gota a gota a un recipiente separado que contenía (S)-4-bencil-2-oxazolidinona (10.81 g., 61 mmoles), DMAP (7.1 g, 58.1 mmoles), Et3N (20.24 ml, 145.3 mmoles) y DCM (100 ml) a 0 °C. La mezcla se dejó calentar a t.a. y se agitó a t.a. por 12 horas. Se añadió agua (300 ml). La capa orgánica se separó y se lavó con HCl 1N (200 ml), solución acuosa saturada de bicarbonato de sodio (200 ml) y salmuera, y se secó (MgSO4), se filtró y se concentró al vacío. El residuo se purificó por cromatografía instantánea (gel de sílice 5-40 % de EtOAc en hexano, elución con gradiente) para proporcionar 99a (11.48 g) como cristales blancos y 99b (10.75 g) como una espuma blanca. Nota: la asignación estereoquímicas de 99ª y 99b es arbitraria.

Compuesto 99a: ^{1}H NMR ($CDCl_3$) δ 1.17-1.34 (m, 5H), 1.45-2.01 (m, 7H), 2.49(tt, J = 12.3 Hz, J = 3.5 Hz, 1H), 2.81 (dd, J = 9.6 Hz, J = 13.2 Hz, 1H), 3.33 (dd, J = 3.2 Hz, J = 13.4 Hz, 1H), 3.74 (quin, J = 7.0 Hz, 1H), 4.19-4.25 (m, 2H), 4.70-4.76 (m, 1H), 7.19- 7.39 (m, 10H).

Compuesto 99b: ^{1}H NMR ($CDCl_3$) δ 1.21 (d, J = 6.9 Hz, 3

H), 1.25-2.02 (m, 9H), 2.51 (tt, J = 12.1 Hz, J = 3.4 Hz, 1H), 2.74 (dd, J = 10.0 Hz, J = 13.2 Hz, 1H), 3.40 (dd, J = 3.4 Hz, J = 13.2 Hz, 1H), 3.78 (quin, J = 6.8 Hz, 1H), 4.12-4.21 (m, 2H), 4.72-4.79 (m, 1H), 7.19-7.39, 10H).

Compuesto 100a. A una solución agitada de 99a (10.48 g, 26.8 mmoles) en THF (400 ml) y agua (125 ml) a 0 °C se añadió hidróxido de litio (1.28 g, 53.6 mmoles) y peróxido de hidrógeno al 3 % (10.7 ml). La mezcla se agitó a 0 °C por 75 minutos y se añadió una solución acuosa de sulfito de sodio (14.75 g en 80 ml de agua), seguido por solución acuosa 0.5 M de bicarbonato de sodio (270 ml). La capa acuosa se lavó con DCM y se acidificó a pH de 1 con HCl 5N y se extrajo con EtOAc. La capa de acetato de etilo se secó ($MgSO_4$), se filtró y concentró al vacío para producir 100a (1 g) como un sólido blanco.

Podría obtenerse material adicional a partir de la capa de DCM.

^1H NMR ($CDCl_3$) δ 1.22 (d, J = 7.2 Hz, 3H), 1.23-1.33 (m, 2H), 1.50.1.56 (m, 2H), 1.58-1.65 (m, 1H), 1.87-2.01 (m, 4H), 2.38 (quin, J = 6.8 Hz, 1H), 2.50 (tt, J = 3.2 Hz, J = 12.0 Hz, 1H), 7.18-7.33 (m, 5H).

Compuesto 100b. El Compuesto 100b (ent-100a) se preparó a partir de 99b de una manera similar a la preparación de 100a a partir de 99a anterior.

Compuesto 101a. El Compuesto 101a se preparó a partir

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de 100a de una manera similar a la descrita para la conversión de 3 a 4 (Ejemplo 2).

^{1}H NMR ($CDCl_3$) δ 1.23 (d, J = 7.2 Hz, 3H), 1.29-1.33 (m,2H), 1.42-1.59 (m, 2H), 1.69-1.80 (m, 2H), 1.85-2.00 (m, 3H), 2.30- 2.39 (m, 1H), 2.45-2.60 (m, 1H), 7.21-7.34 (m, 5H).

Compuesto 101b. El Compuesto 101b (ent-101a) se preparó a partir de 100b de la misma manera que la preparación de 101a a partir de 100a anterior.

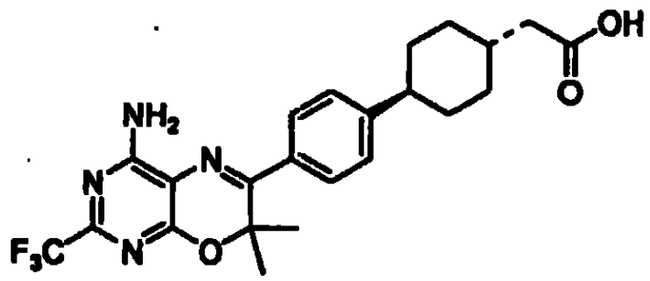
Ejemplo 9. El ejemplo 9, se preparó a partir de 101a y 4, 5- diamino- 6- hidroxi- 2- metilpirimidina (P.D. Landauer y colaboradores, J. Chem. Soc., 1953, 3721) de una manera similar a la descrita para la conversión de 4 al Ejemplo 2.

^{1}H NMR ($CDCl_3$) δ 1.24 (d, J=6.8 Hz, 3H), 1.25-1.30 (m, 2H), 1.48-1.59 (m, 3H), 1.71 (s, 6H), 1.91-2.00 (m, 4H), 2.36-2.40 (m, 1H), 2.46 (s, 3H), 2.51-2.57 (m, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H). Espectro de Masa (ESI+) m/e = 423.3 (M+1).

Ejemplo 9-2. El ejemplo 9-2 (ent-Ej. 9) se preparó a partir de 101b de una manera similar a la preparación del Ejemplo 9 a partir de 101a anterior.

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Ejemplo 9-3:



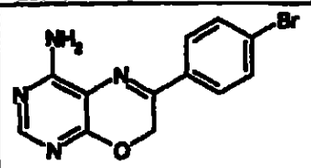
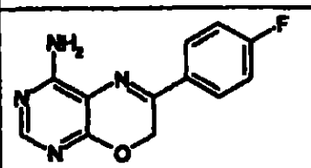
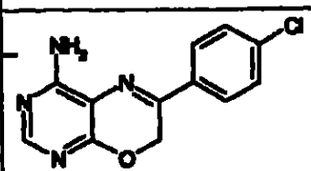
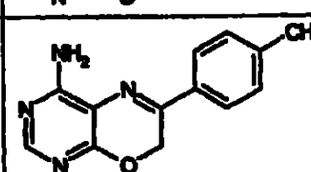
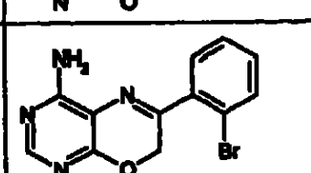
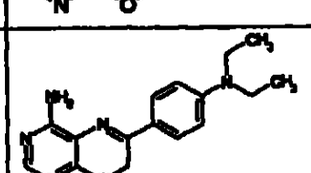
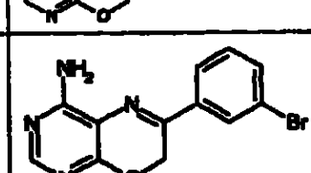
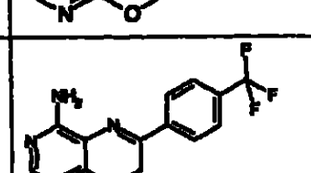
Este compuesto se obtuvo de la misma manera que en el Ejemplo 9.

1H NMR (DMSO-d_6) δ 1.10-1.20 (m, 2H), 1.42-1.90 (m, 13H), 2.17 (d, J = 6.8 Hz, 2H), 2.45-2.60 (m, 1H), 7.34 (d, J = 8 Hz, 2H), 7.36 (brs, 1H), 7.71 (d, J = 8Hz, 2H), 7.74 (brs, 1H), 12.04 (brs, 1H).

Los compuestos propcrcionados en la Tabla 10 se prepararon por combinación de los métodos proporcionados anteriormente.

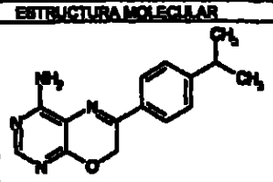
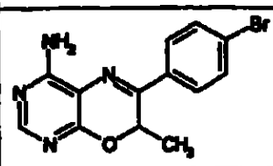
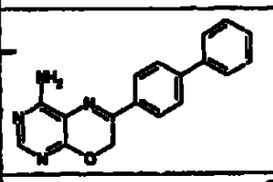
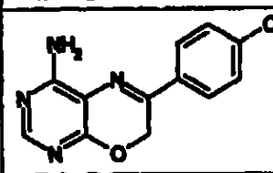
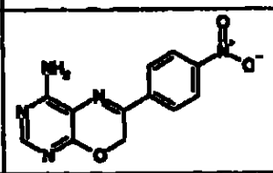
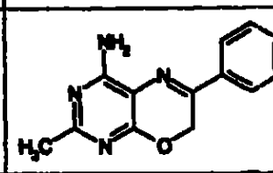
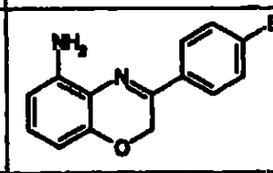
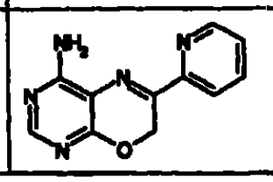
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Tabla 10.

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
1		>200	5.44(s, 2H), 7.10(bs, 2H), 7.58(d, 2H, J=8.6Hz), 7.93(s, 1H), 8.02(d, 2H, J=8.6Hz).	DMSO-d6, 400MHz
1-2		>220	5.48(s, 2H), 7.08(bs, 2H), 7.35(t, 2H, J=7.6Hz), 7.94(s, 1H), 8.15-8.19(m, 2H)	DMSO-d6, 400
1-3		>220	5.48(s, 2H), 7.12(bs, 2H), 7.57(d, 2H, J=8.6Hz), 7.94(s, 1H), 8.13(d, 2H, J=8.6Hz)	DMSO-d6, 400
1-4		217-219	2.39(s, 3H), 5.43(s, 2H), 7.33(bs, 2H), 7.33(d, 2H, J=8.0Hz), 7.93(s, 1H), 7.99(d, 2H, J=8.0Hz)	DMSO-d6, 400
1-5			5.52(s, 2H), 7.03(bs, 2H), 7.46(t, 1H, J=8.0Hz), 7.53(t, 1H, J=4.0Hz), 7.64(d, 1H, J=8.0Hz), 7.76(d, 1H, J=8.0Hz), 7.89(s, 1H)	DMSO-d6, 400
1-6		208dec.	1.14(t, 6H, J=8.0Hz), 3.44(q, 4H, J=8.0Hz), 5.34(s, 2H), 6.72(d, 2H, J=8.0Hz), 6.84(bs, 2H), 7.88(s, 1H), 7.90(d, 2H, J=8.0Hz)	DMSO-d6, 400
1-7		>220	5.45(s, 2H), 7.10(bs, 2H), 7.46(t, 1H, J=8.0Hz), 7.72(d, 1H, J=8.0Hz), 7.93(s, 1H), 8.01(d, 1H, J=8.0Hz), 8.30(s, 1H)	DMSO-d6, 400
1-8		>220	5.51(s, 2H), 7.10(bs, 2H), 7.88(d, 2H, J=8.0Hz), 7.95(s, 1H), 8.30(d, 2H, J=8.0Hz)	DMSO-d6, 400

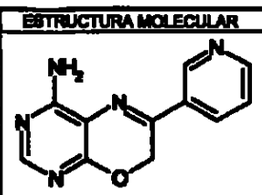
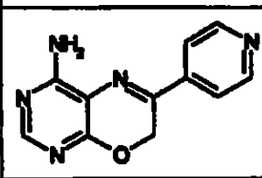
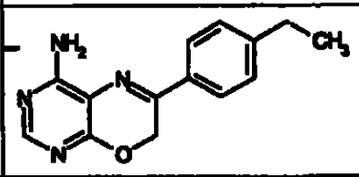
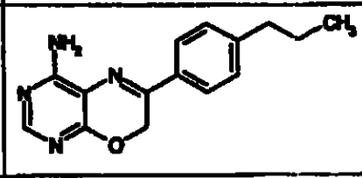
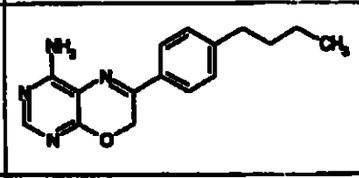
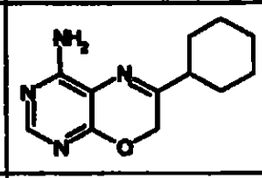
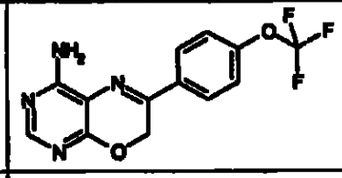
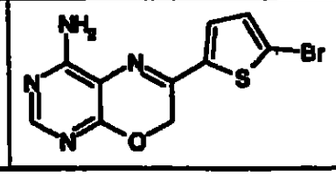
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Tabla 1 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
1-9		176-178	1.23(d, 6H, J=6.0Hz), 2.93-3.00(m, 1H), 5.40(s, 2H), 7.01(m, 2H), 7.35(d, 2H, J=6.0Hz), 7.52(s, 1H), 7.59(d, 2H, J=6.0Hz)	DMSO-d6, 400
1-10		222 - 224	1.53(d, 3H, J=6.0Hz), 5.06(q, 1H, J=6.0Hz), 7.14(bm, 2H), 7.59(d, 2H, J=6.0Hz), 7.93(s, 1H), 8.09(d, 2H, J=6.0Hz)	DMSO-d6, 400
1-11		>250	5.46(s, 2H), 7.06(bm, 2H), 7.39-7.43(m, 1H), 7.48-7.52(m, 2H), 7.78-7.81(m, 4H), 7.93(s, 1H), 8.19(d, 2H, J=6.0Hz)	DMSO-d6, 400
1-12		191 - 193	3.84(s, 3H), 5.40(s, 2H), 6.98(bm, 2H), 7.03(d, 2H, J=6.0Hz), 7.90(s, 1H), 8.05(d, 2H, J=6.0Hz)	DMSO-d6, 400
1-13		>250	5.60(s, 2H), 7.35(bm, 2H), 7.66(s, 1H), 8.20(d, 2H, J=6.0Hz), 8.34(d, 2H, J=6.0Hz)	DMSO-d6, 400
1-14		>220	2.35(s, 3H), 5.40(s, 2H), 7.52(bm, 2H), 7.70(d, 2H, J=6.0Hz), 8.03(d, 2H, J=6.0Hz)	DMSO-d6, 300
1-15		76 - 77	5.05(s, 2H), 5.58(bm, 2H), 6.08(dd, 1H, J=1.1, 8.0 Hz), 6.32(dd, 1H, J=1.1, 8.0 Hz), 6.83(t, 1H, J=8.0 Hz), 7.60(d, 2H, J=8.8 Hz), 8.04(d, 2H, J=8.8 Hz).	DMSO-d6, 300MHz
1-16		216	5.66(s, 2H), 7.32(br, 2H), 7.51-7.55(m, 1H), 7.95-8.00(m, 2H), 8.53-8.55(m, 1H), 8.65-8.67(m, 1H)	DMSO-d6, 300

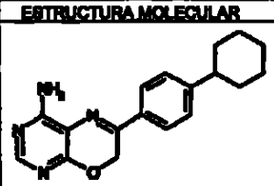
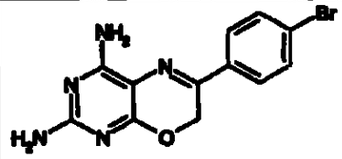
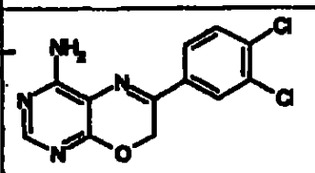
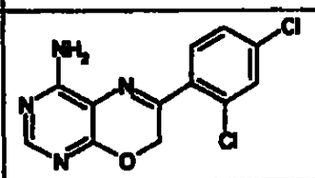
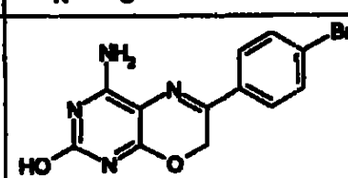
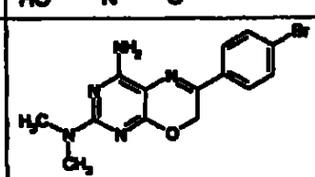
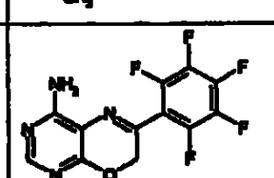
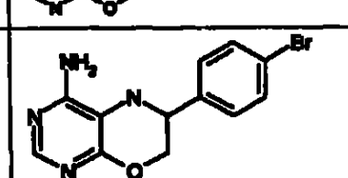
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Tabla 1 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
1-17		>220	5.43(s, 2H), 7.31(brs, 2H), 7.51-7.55(m, 1H), 7.94(s, 1H), 8.44-8.48(m, 1H), 8.68-8.70(m, 1H), 9.27(s, 1H)	DMSO-d6, 300
1-18		>220	5.43(s, 2H), 7.26(br, 2H), 7.99(s, 1H), 8.01(d, 2H, J=6.0Hz), 8.73(d, 2H, J=6.0Hz)	DMSO-d6, 300
1-19		191 - 193	1.21(t, 3H, J=7.5Hz), 2.68(q, 2H, J=7.5Hz), 5.42(s, 2H), 7.07(brs, 2H), 7.34(d, 2H, J=8.0Hz), 7.92(s, 1H), 8.01(d, 2H, J=8.0Hz)	DMSO-d6, 300
1-20		189 - 192	0.90(t, 3H, J=7.5Hz), 1.55-1.66(m, 2H), 2.60-2.66(m, 2H), 5.43(s, 2H), 7.07(brs, 2H), 7.33(d, 2H, J=8.0Hz), 7.92(s, 1H), 8.01(d, 2H, J=8.0Hz)	DMSO-d6, 300
1-21		183 - 186	0.91(t, 3H, J=7.5Hz), 1.37-1.57(m, 2H), 1.63-1.83(m, 2H), 2.63-2.67(m, 2H), 5.43(s, 2H), 7.08(brs, 2H), 7.32(d, 2H, J=8.0Hz), 7.92(s, 1H), 8.00(d, 2H, J=8.0Hz)	DMSO-d6, 400
1-22		142	1.14-1.46(m, 6H), 1.61-1.83(m, 6H), 2.23-2.30(m, 1H), 4.69(s, 2H), 6.74(brs, 2H), 7.87(s, 1H)	DMSO-d6, 400
1-23		209 - 212	5.47(s, 2H), 7.17(brs, 2H), 7.40(d, 2H, J=8.0Hz), 7.94(s, 1H), 8.22(d, 2H, J=8.0Hz)	DMSO-d6, 300
1-24			5.39(s, 2H), 6.93(brs, 2H), 7.35(d, 2H, J=8.0Hz), 7.52(d, 2H, J=3.0Hz), 7.92(s, 1H)	DMSO-d6, 300

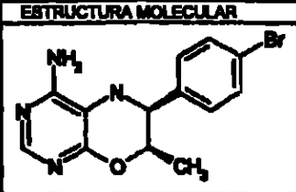
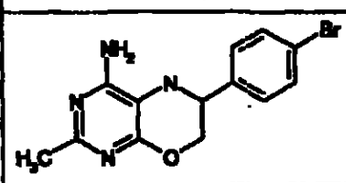
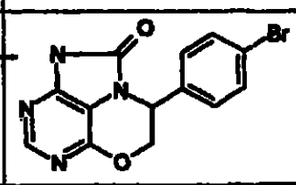
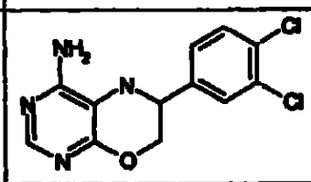
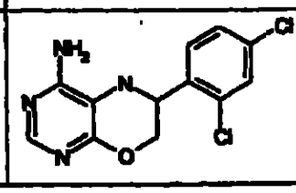
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Tabla 1 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
1-25		219 - 221	1.23-1.51(m, 6H), 1.66-1.85(m, 5H), 2.65-2.83(m, 1H), 6.43(s, 2H), 7.08(brs, 2H), 7.58(s, 1H), 8.00(d, 2H, J=8.0Hz)	DMSO-d6, 300
1-26		>220	6.25(s, 2H), 6.34(brs, 2H), 6.88(brs, 2H), 7.63(d, 2H, J=12.0Hz), 7.98(d, 2H, J=12.0Hz)	DMSO-d6, 400
1-27		>220	6.48(s, 2H), 7.20(brs, 2H), 7.77(d, 1H, J=8.0Hz), 7.94(s, 1H), 8.02(d, 1H, J=8.0Hz), 8.46(s, 1H)	DMSO-d6, 300
1-28		216 - 220	6.22(s, 2H), 7.17(brs, 2H), 7.57-7.60(m, 1H), 7.75-7.78(m, 2H), 7.99(s, 1H)	DMSO-d6, 300
1-29		>220	6.35(s, 2H), 7.16(brs, 2H), 7.85(d, 2H, J=8.0Hz), 7.92(d, 2H, J=8.0Hz), 10.87(brs, 1H)	DMSO-d6, 400
1-30		>220	3.04(s, 6H), 6.27(s, 2H), 6.73(brs, 2H), 7.63(d, 2H, J=8.0Hz), 7.94(d, 2H, J=8.0Hz)	DMSO-d6, 400
1-31		190 - 192	6.17(s, 2H), 6.81(s, 1H)	DMSO-d6, 300
1-32		>200	4.07(dd, 1H, J=7.8, 10.7 Hz), 4.33(dd, 1H, J=1.8, 10.7 Hz), 4.46(m, 1H), 6.19(brs, 1H), 6.27(brs, 2H), 7.40(d, 2H, J=8.6 Hz), 7.58(s, 1H), 7.80(d, 2H, J=8.6 Hz).	DMSO-d6, 400MHz

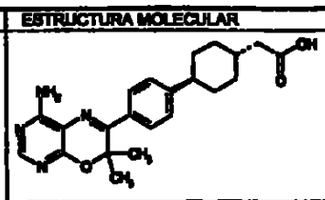
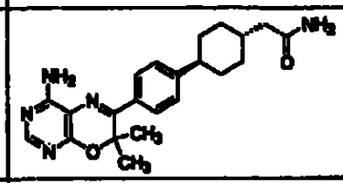
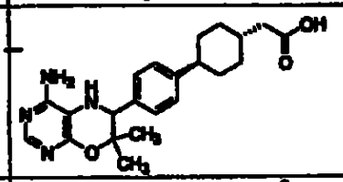
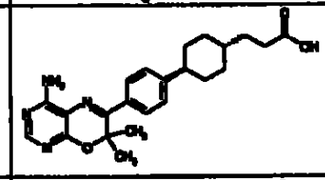
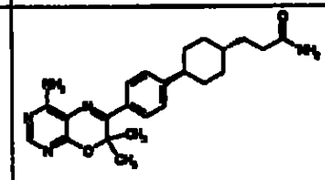
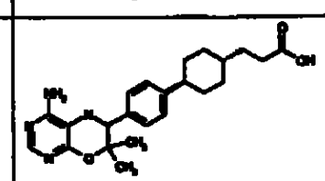
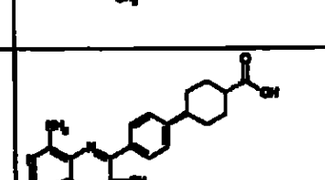
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Tabla 1 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
1-33			0.99(d, 3H, J=6.6Hz), 4.54(bs, 2H), 5.36(qr, 1H), 6.38(br, 2H), 7.28(d, 2H, J=8.0Hz), 7.58(d, 2H, J=8.0Hz), 7.88(s, 1H)	DMSO-d6, 300
1-34		232 - 233	2.16(s, 3H), 4.03-4.08(m, 1H), 4.29-4.32(m, 1H), 4.42-4.45(m, 1H), 4.88(bra, 1H), 6.19(bra, 2H), 7.40(d, 2H, J=8.0Hz), 7.59(d, 2H, J=8.0Hz)	DMSO-d6, 400
1-35		>220	4.66-4.75(m, 2H), 5.46-5.49(m, 1H), 7.28(d, 2H, J=8.0Hz), 7.60(d, 2H, J=8.0Hz), 8.30(s, 1H), 11.84(bra, 1H)	DMSO-d6, 300
1-36		198 - 200	4.09-4.15(m, 1H), 4.34-4.36(m, 1H), 4.54(bra, 1H), 6.23(bra, 1H), 6.35(bra, 2H), 7.45(d, 1H, J=12.0Hz), 7.83(s, 1H), 7.89(d, 1H, J=8.0Hz), 7.74(s, 1H)	DMSO-d6, 300
1-37		>220	4.02-4.09(m, 1H), 4.34-4.36(m, 1H), 4.80(bra, 1H), 6.29(bra, 1H), 6.30(bra, 2H), 7.51(s, 2H), 7.84(s, 1H), 7.70(s, 1H)	DMSO-d6, 300

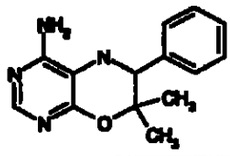
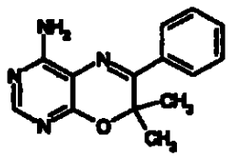
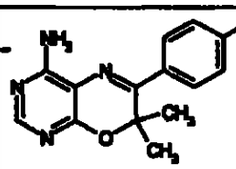
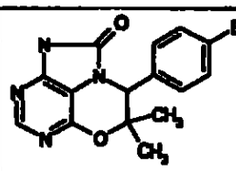
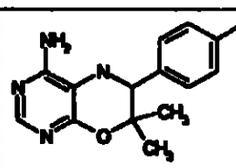
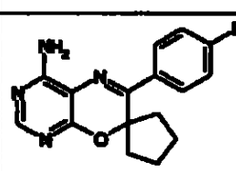
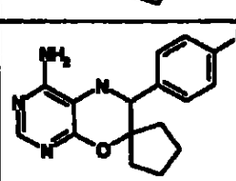
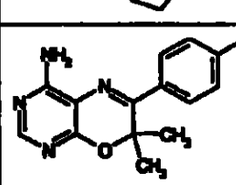
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Tabla 2

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2		>270	1.07-1.21(m, 2H), 1.48-1.84(m, 13H), 2.15(d, 2H, J=6.0Hz), 2.53-2.58(m, 1H), 6.97(bm, 2H), 7.31(d, 2H, J=8.0Hz), 7.65(d, 2H, J=8.0Hz), 7.95(s, 1H), 11.98(bm, 1H)	DMSO-d6, 300
2-2		224 - 226	1.08-1.17(m, 2H), 1.4-1.53(m, 2H), 1.61(s, 6H), 1.68-1.87(m, 5H), 1.98(d, 2H, J=7.12Hz), 2.53(m, 1H), 6.67(br, 1H), 6.89(br, 2H), 7.21(br, 1H), 7.3(d, 2H, J=8.12Hz), 7.83(d, 2H, J=8.12Hz), 7.94(s, 1H)	DMSO-d6, 400
2-3		273 - 279	1.03-1.22(m, 6H), 1.4-1.48(m, 2H), 1.7-1.83(m, 5H), 2.14(d, 2H, J=6.83Hz), 2.54(m, 1H), 4.11(br, 1H), 6.27(br, 1H), 6.23(br, 2H), 7.25(d, 2H, J=8.07Hz), 7.33(d, 2H, J=8.04Hz), 7.81(s, 1H), 11.75(br, 1H)	DMSO-d6, 300
2-4		>250	1.04-1.08(m, 2H), 1.43(m, 1H), 1.43-1.50(m, 4H), 1.50(s, 6H), 1.83(brd, 4H, J=11.4 Hz), 2.28(t, 2H, d=7.7 Hz), 2.50(m, 1H), 6.89(brs, 2H), 7.29(d, 2H, J=8.3 Hz), 7.83(d, 2H, J=8.3 Hz), 7.94(s, 1H), 11.84(brs, 1H).	DMSO-d6, 400MHz
2-5		244 - 248	1.04-1.08(m, 2H), 1.28(m, 1H), 1.40-1.48(m, 4H), 1.50(s, 6H), 1.83(brd, 4H, J=10.2 Hz), 2.08(t, 2H, d=7.4 Hz), 2.50(m, 1H), 6.89(brs, 1H), 6.98(brs, 2H), 7.29(brs, 1H), 7.29(d, 2H, J=8.3 Hz), 7.83(d, 2H, J=8.3 Hz), 7.94(s, 1H).	DMSO-d6, 400MHz
2-6		>250	1.04-1.08(m, 2H), 1.08(s, 3H), 1.22(s, 3H), 1.32(m, 1H), 1.43-1.48(m, 4H), 1.83(brd, 4H, J=10.7 Hz), 2.24(t, 2H, d=7.7 Hz), 2.50(m, 1H), 4.11(s, 1H), 5.39(s, 1H), 6.22(brs, 2H), 7.23(d, 2H, J=8.1 Hz), 7.35(d, 2H, J=8.1 Hz), 7.83(s, 1H), 11.72(brs, 1H).	DMSO-d6, 400MHz
2-7		>250	1.43-1.55(m, 4H), 1.50(s, 6H), 1.81-1.91(m, 2H), 1.95-2.08(m, 2H), 2.23-2.33(m, 1H), 2.52-2.60(m, 1H), 6.90(br, 2H), 7.30(d, 2H, J=8.1Hz), 7.84(d, 2H, J=8.1Hz), 7.95(s, 1H)	DMSO-d6, 400MHz

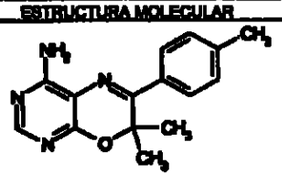
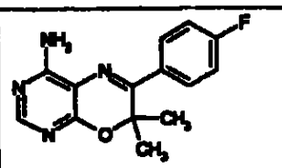
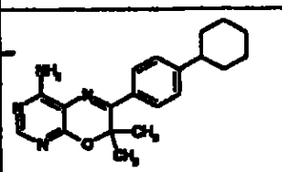
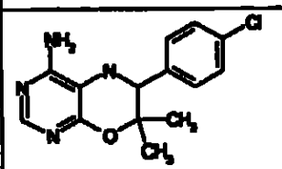
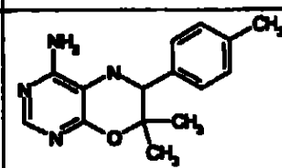
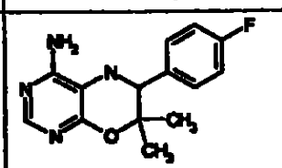
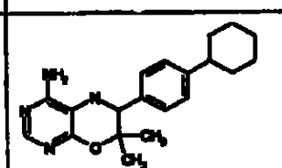
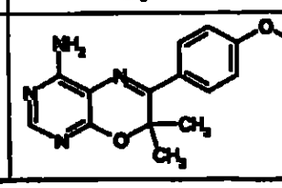
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-8		>220	1.07(s, 3H), 1.23(s, 3H), 4.17(bra, 1H), 5.31(bra, 1H), 6.29(bra, 2H), 7.35-7.47(m, 5H), 7.53(s, 1H)	DMSO-d6, 300
2-9		169 - 190	1.59(s, 6H), 6.83(bra, 2H), 7.44-7.50(m, 3H), 7.69-7.71(m, 2H), 7.96(s, 1H)	DMSO-d6, 400
2-10		201 - 203	1.60(s, 6H), 7.03(bra, 2H), 7.66(d, 2H, J=8.0Hz), 7.70(d, 2H, J=8.0Hz), 7.98(s, 1H)	DMSO-d6, 300
2-11		>220	1.23(s, 3H), 1.47(s, 3H), 5.38(s, 2H), 6.66(d, 2H, J=8.0Hz), 7.58(d, 2H, J=8.0Hz), 8.36(s, 1H), 11.84(bra, 1H)	DMSO-d6, 400
2-12		>220	1.03(s, 3H), 1.23(s, 3H), 4.20(bra, 1H), 5.33(bra, 1H), 6.36(bra, 2H), 7.40(d, 2H, J=8.0Hz), 7.60(d, 2H, J=8.0Hz), 7.63(s, 1H)	DMSO-d6, 300
2-13		184 - 186	1.76-1.86(m, 2H), 2.01-2.08(m, 1H), 2.13-2.19(m, 1H), 7.05(bra, 2H), 7.61(d, 2H, J=8.0Hz), 7.66(d, 2H, J=8.0Hz), 7.85(s, 1H)	DMSO-d6, 400
2-14		228 - 233	1.39-1.76(m, 4H), 4.37(bra, 1H), 5.51(bra, 1H), 6.33(bra, 2H), 7.27(d, 2H, J=8.0Hz), 7.65(d, 2H, J=8.0Hz), 7.83(s, 1H)	DMSO-d6, 300
2-15		210 - 211	1.60(s, 6H), 7.06(bra, 2H), 7.53(d, 2H, J=8.0Hz), 7.77(d, 2H, J=8.0Hz), 7.98(s, 1H)	DMSO-d6, 300

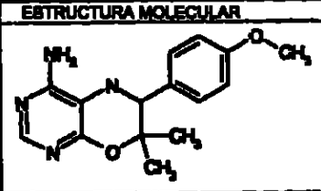
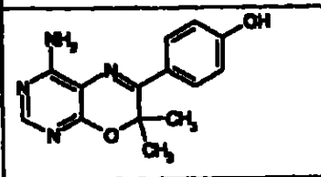
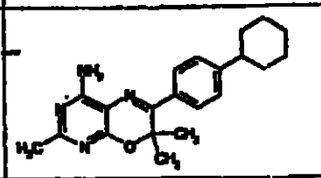
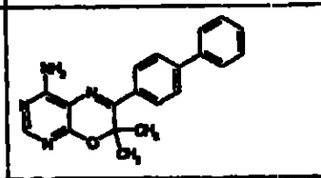
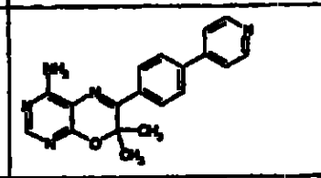
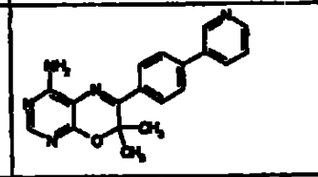
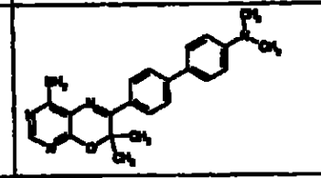
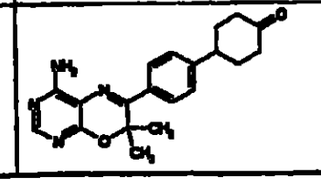
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Tabla 2 (Continuación)

NUEVO EJEMPLO Nº	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-16		161 - 162	1.82(s, 6H), 2.36(s, 3H), 6.57(brs, 2H), 7.27(d, 2H, J=8.0Hz), 7.63(d, 2H, J=8.0Hz), 7.96(s, 1H)	DMSO-d6, 300
2-17		189 - 190	1.80(s, 6H), 7.01(brs, 2H), 7.28(dd, 2H, J=8.0, 8.0Hz), 7.51(dd, 2H, J=8.0, 8.0Hz), 7.99(s, 1H)	DMSO-d6, 300
2-18		186 - 187	1.21-1.47(m, 5H), 1.80(s, 6H), 1.70-1.82(m, 5H), 2.54-2.68(m, 1H), 6.59(brs, 2H), 7.29(d, 2H, J=8.0Hz), 7.54(d, 2H, J=8.0Hz), 7.94(s, 1H)	DMSO-d6, 400
2-19		>230	1.68(s, 3H), 1.23(s, 3H), 4.21(brs, 1H), 6.33(brs, 1H), 6.59(brs, 2H), 7.46(s, 4H), 7.83(s, 1H)	DMSO-d6, 300
2-20		>230	1.68(s, 3H), 1.21(s, 3H), 2.31(s, 3H), 4.12(brs, 1H), 6.29(brs, 1H), 6.27(brs, 2H), 7.20(d, 2H, J=8.0Hz), 7.34(d, 2H, J=8.0Hz), 7.82(s, 1H)	DMSO-d6, 300
2-21		>230	1.68(s, 3H), 1.23(s, 3H), 4.20(brs, 1H), 6.29(brs, 1H), 6.22(brs, 2H), 7.22(dd, 2H, J=8.0, 8.0Hz), 7.48(dd, 2H, J=8.0, 8.0Hz), 7.83(s, 1H)	DMSO-d6, 400
2-22		>230	1.08(s, 3H), 1.22(s, 3H), 1.25-1.46(m, 6H), 1.69-1.83(m, 6H), 2.47-2.64(m, 1H), 4.11(brs, 1H), 6.28(brs, 1H), 6.39(brs, 2H), 7.25(d, 2H, J=8.0Hz), 7.37(d, 2H, J=8.0Hz), 7.81(s, 1H)	DMSO-d6, 300
2-23		183 - 184	1.81(s, 6H), 3.82(s, 3H), 6.57(brs, 2H), 6.99(d, 2H, J=8.0Hz), 7.71(d, 2H, J=8.0Hz), 7.94(s, 1H)	DMSO-d6, 400

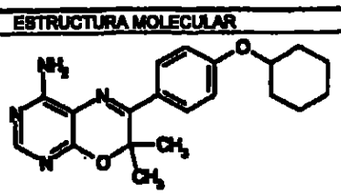
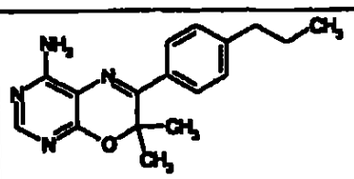
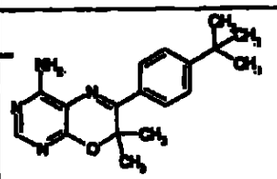
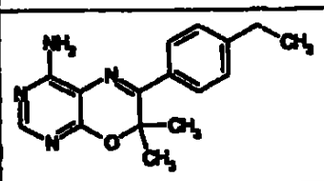
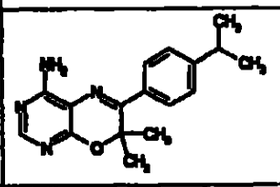
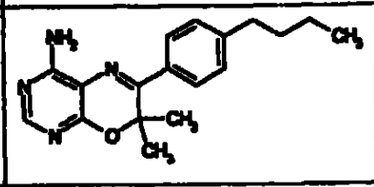
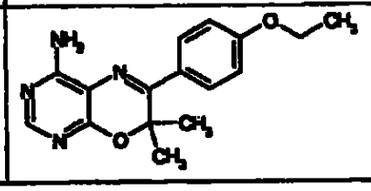
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-24		225 - 226	1.06(s, 3H), 1.21(s, 3H), 3.76(s, 3H), 4.11(bra, 1H), 6.23(bra, 1H), 6.38(bra, 2H), 6.66(d, 2H, J=8.0Hz), 7.38(d, 2H, J=8.0Hz), 7.62(s, 1H)	DMSO-d6, 300
2-25		245 - 248	1.60(s, 6H), 6.62(d, 2H, J=8.0Hz), 6.91(bra, 2H), 7.63(d, 2H, J=8.0Hz), 7.53(s, 1H), 9.94(s, 1H)	DMSO-d6, 300
2-26		226 - 227	1.18-1.46(m, 6H), 1.58(s, 6H), 1.69-1.82(m, 6H), 2.26(s, 3H), 2.53-2.58(m, 1H), 6.58(bra, 2H), 7.29(d, 2H, J=8.0Hz), 7.52(d, 2H, J=8.0Hz)	DMSO-d6, 300
2-27		218 - 219	1.58(s, 6H), 7.03(bra, 2H), 7.36-7.52(m, 3H), 7.73-7.77(m, 4H), 7.83-7.86(m, 2H), 7.97(s, 1H)	DMSO-d6, 300
2-28		>250	1.55(s, 6H), 6.97(bra, 2H), 7.77(d, 2H, J=8.0Hz), 7.55(s, 4H), 7.97(s, 1H), 8.58(d, 2H, J=8.0Hz)	DMSO-d6, 300
2-29		231 - 232	1.55(s, 6H), 7.02(bra, 2H), 7.51-7.55(m, 1H), 7.83(s, 2H, J=8.0Hz), 7.86(d, 2H, J=8.0Hz), 7.98(s, 1H), 8.14-8.18(m, 1H), 8.81-8.83(m, 1H), 8.97-8.98(m, 1H)	DMSO-d6, 300
2-30		210 - 211	1.55(s, 6H), 2.56(s, 6H), 6.83(d, 2H, J=8.0Hz), 6.98(bra, 2H), 7.50(d, 2H, J=8.0Hz), 7.57(d, 2H, J=8.0Hz), 7.78(d, 2H, J=8.0Hz), 7.96(s, 1H)	DMSO-d6, 300
2-31		>240	1.61(s, 6H), 1.89-2.13(m, 4H), 2.28-2.34(m, 2H), 2.86-2.92(m, 2H), 3.09-3.17(m, 1H), 6.97(bra, 2H), 7.38(d, 2H, J=8.0Hz), 7.66(d, 2H, J=8.0Hz), 7.99(s, 1H)	DMSO-d6, 300

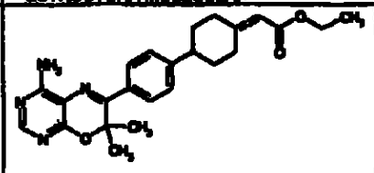
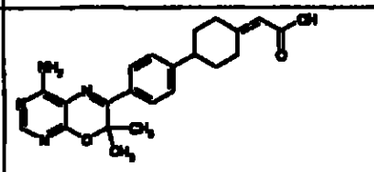
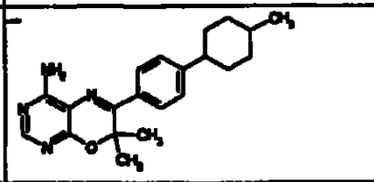
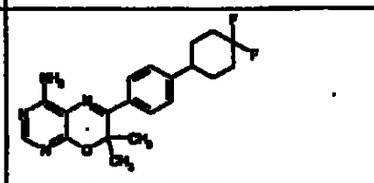
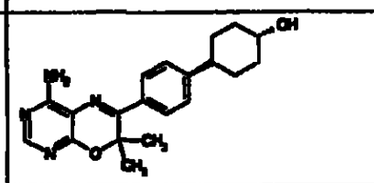
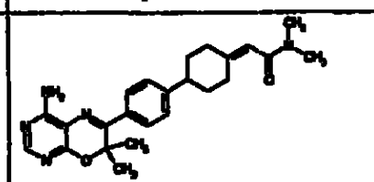
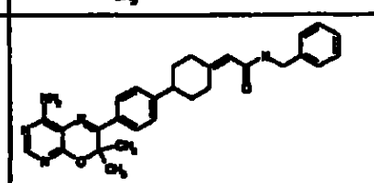
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-32		174 - 175	1.35-1.55(m, 7H), 1.61(s, 6H), 1.70-1.76(m, 2H), 1.92-1.96(m, 2H), 6.89(brs, 2H), 6.97(d, 2H, J=8.0Hz), 7.59(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400
2-33		185 - 186	0.91(t, 3H, J=6.0Hz), 1.57-1.66(m, 2H), 1.60(s, 6H), 2.51(t, 2H, J=8.0Hz), 6.89(br, 2H), 7.27(d, 2H, J=8.0Hz), 7.63(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-34		220 - 220	1.39(s, 9H), 1.67(s, 6H), 7.49(d, 2H, J=8.0Hz), 7.59(br, 2H), 7.70(d, 2H, J=8.0Hz), 8.15(s, 1H)	DMSO-d6, 400MHz
2-35		135 - 136	1.21(t, 3H, J=7.0Hz), 1.60(s, 6H), 2.66(q, 2H, J=7.0Hz), 6.90(br, 2H), 7.29(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 400MHz
2-36		175 - 179	1.23(d, 6H, J=6.0Hz), 1.61(s, 6H), 2.91-2.99(m, 1H), 6.89(br, 2H), 7.32(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 400MHz
2-37		157 - 160	0.91(t, 3H, J=6.0Hz), 1.27-1.39(m, 2H), 1.54-1.61(m, 2H), 1.60(s, 6H), 2.62(t, 2H, J=8.0Hz), 6.90(br, 2H), 7.27(d, 2H, J=8.0Hz), 7.63(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 400MHz
2-38		189 - 190	1.35(t, 3H, J=6.0Hz), 1.61(s, 6H), 4.10(q, 2H, J=6.7Hz), 6.87(brs, 2H), 6.97(d, 2H, J=8.0Hz), 7.70(d, 2H, J=12.0Hz), 7.93(s, 1H)	DMSO-d6, 400

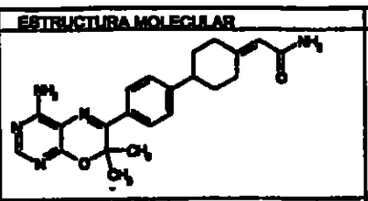
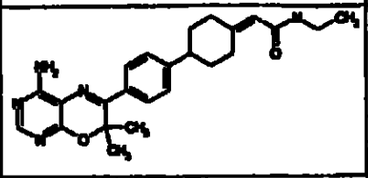
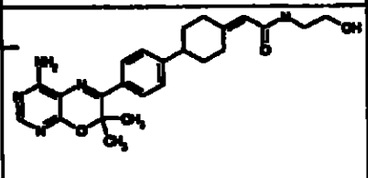
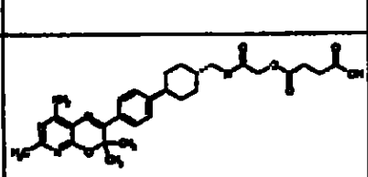
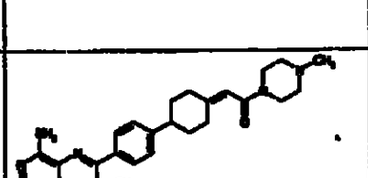
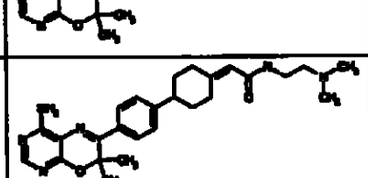
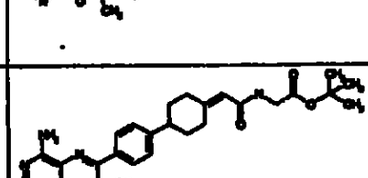
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-39		207 - 208	1.21(t, 3H, J=7.5Hz), 1.48-1.68(m, 6H), 1.93-2.08(m, 2H), 2.33-2.48(m, 2H), 2.84-2.94(m, 1H), 3.85-3.90(m, 1H), 4.09(q, 2H, J=7.5Hz), 5.72(s, 1H), 6.97(brs, 2H), 7.33(d, 2H, J=8.0Hz), 7.85(d, 2H, J=8.0Hz), 7.85(s, 1H)	DMSO-d6, 300
2-40		>250	1.48-1.63(m, 6H), 1.97-2.04(m, 2H), 2.32-2.38(m, 2H), 2.84-2.94(m, 1H), 3.85-3.90(m, 1H), 5.64(s, 1H), 6.90(brs, 2H), 7.32(d, 2H, J=8.0Hz), 7.84(d, 2H, J=8.0Hz), 7.84(s, 1H), 11.80(brs, 1H)	DMSO-d6, 400
2-41		201 - 209	0.93(d, 3H, J=6.8Hz), 1.03-1.13(m, 2H), 1.39-1.57(m, 3H), 1.62(s, 6H), 1.76-1.87(m, 4H), 2.49-2.58(m, 1H), 6.91(br, 2H), 7.31(d, 2H, J=8.4Hz), 7.76(d, 2H, J=8.4Hz), 7.86(s, 1H)	DMSO-d6, 400MHz
2-42		225 - 227	1.60(s, 6H), 1.64-1.74(m, 2H), 1.89-2.16(m, 6H), 2.75-2.81(m, 1H), 6.90(brs, 2H), 7.33(d, 2H, J=8.0Hz), 7.85(d, 2H, J=8.0Hz), 7.86(s, 1H)	DMSO-d6, 400
2-43		246 - 248	1.23-1.35(m, 2H), 1.43-1.58(m, 2H), 1.60(s, 6H), 1.75-1.81(m, 2H), 1.90-1.95(m, 2H), 2.46-2.54(m, 1H), 4.90(d, 1H, J=8.0Hz), 6.97(brs, 2H), 7.30(d, 2H, J=8.0Hz), 7.84(d, 2H, J=8.0Hz), 7.85(s, 1H)	DMSO-d6, 300
2-44			1.48-1.60(m, 2H), 1.60(s, 6H), 1.90-2.00(m, 2H), 2.25-2.40(m, 2H), 2.85(s, 3H), 3.00(s, 3H), 3.13(m, 1H), 5.58(s, 1H), 6.90(brs, 2H), 7.31(d, 2H, J=8.3 Hz), 7.84(d, 2H, J=8.3 Hz), 7.94(s, 1H).	DMSO-d6, 400MHz
2-45		142 - 144	1.48-1.60(m, 2H), 1.60(s, 6H), 1.90-2.00(m, 2H), 2.25-2.40(m, 2H), 2.80(m, 1H), 4.13(m, 1H), 4.30(d, 2H, J=6.0 Hz), 5.58(s, 1H), 6.90(brs, 2H), 7.20-7.33(m, 6H), 7.84(d, 2H, J=8.3 Hz), 7.94(s, 1H), 8.30(brt, 1H, J=6.0Hz).	DMSO-d6, 400MHz

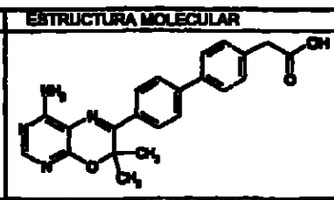
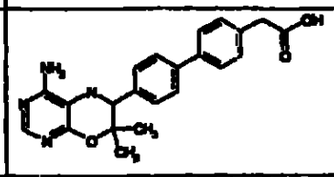
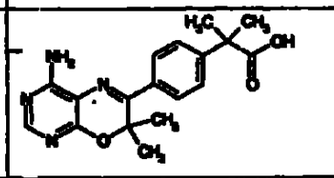
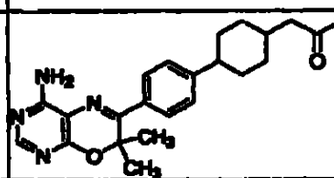
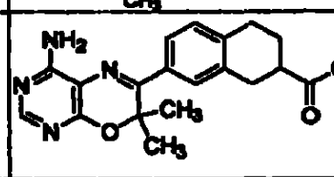
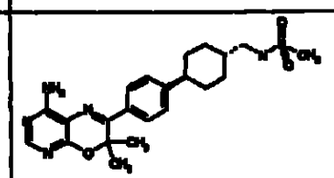
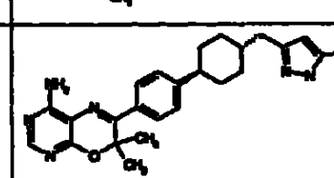
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-46			1.45-1.57(m, 2H), 1.66(s, 6H), 1.94-2.00(m, 2H), 2.23-2.30(m, 2H), 2.76-2.86(m, 1H), 5.67(s, 1H), 6.77(bs, 1H), 6.97(bs, 2H), 7.28(bs, 1H), 7.33(d, 2H, J=8.5Hz), 7.86(d, 2H, J=8.5Hz), 7.93(s, 1H)	DMSO-d6, 300
2-47		229 - 230	1.03(t, 3H, J=7.5Hz), 1.46-1.56(m, 2H), 1.60(s, 6H), 1.81-2.32(m, 5H), 2.73-2.86(m, 1H), 3.05-3.14(m, 2H), 5.65(s, 1H), 6.97(bs, 2H), 7.32(d, 2H, J=8.5Hz), 7.85(d, 2H, J=8.5Hz), 7.80-7.84(m, 1H), 7.96(s, 1H)	DMSO-d6, 300
2-48			1.45-1.56(m, 2H), 1.60(s, 6H), 1.84-2.02(m, 2H), 2.23-2.30(m, 2H), 2.80-2.86(m, 1H), 3.13-3.19(m, 2H), 3.38-3.43(m, 2H), 4.07-4.14(m, 0.5H), 4.66-4.70(m, 0.5H), 5.69(s, 1H), 6.97(bs, 2H), 7.32(d, 2H, J=8.5Hz), 7.85(d, 2H, J=8.5Hz), 7.84(t, 1H, J=6.0Hz), 7.96(s, 1H)	DMSO-d6, 300
2-49			0.85-1.08(m, 2H), 1.27-1.59(m, 3H), 1.59(s, 6H), 1.78-1.85(m, 4H), 2.33-2.47(m, 1H), 2.63-2.73(m, 2H), 2.77-2.86(m, 2H), 3.08(t, 2H, J=7.0Hz), 4.58(s, 2H), 6.69(t, 1H, J=6.0Hz), 7.11(d, 2H, J=8.3Hz), 7.28(s, 2H), 7.43(d, 2H, J=8.3Hz)	DMSO-d6, 300MHz
2-50			1.41-1.60(m, 2H), 1.60(s, 6H), 1.81-2.03(m, 2H), 2.16-2.42(m, 6H), 2.76-2.86(m, 1H), 2.98-3.05(m, 1H), 3.43-3.49(m, 1H), 3.49(br, 2H), 5.67(s, 1H), 6.89(br, 2H), 7.31(d, 2H, J=8.6Hz), 7.84(d, 2H, J=8.6Hz), 7.94(s, 1H)	DMSO-d6, 400MHz
2-51			1.43-1.56(m, 2H), 1.60(s, 6H), 1.87-2.01(m, 3H), 2.16(s, 6H), 2.28-2.34(m, 4H), 2.78-2.86(m, 1H), 3.18(q, 2H, J=6.4Hz), 4.05-4.10(m, 1H), 5.67(s, 1H), 6.89(br, 2H), 7.31(d, 2H, J=8.1Hz), 7.84(d, 2H, J=8.1Hz), 7.89(t, 1H, J=6.4Hz), 7.94(s, 1H)	DMSO-d6, 400MHz
2-52		212 - 216	1.41(s, 9H), 1.47-1.53(m, 2H), 1.60(s, 6H), 1.88-2.02(m, 3H), 2.28-2.34(m, 2H), 2.82-2.86(m, 1H), 2.74(d, 2H, J=6.1Hz), 3.98-4.05(m, 1H), 5.72(s, 1H), 6.90(br, 2H), 7.31(d, 2H, J=8.1Hz), 7.84(d, 2H, J=8.1Hz), 7.94(s, 1H), 8.11(t, 1H, J=6.1Hz)	DMSO-d6, 400MHz

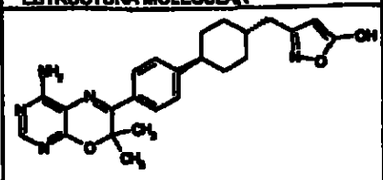
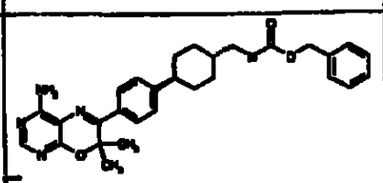
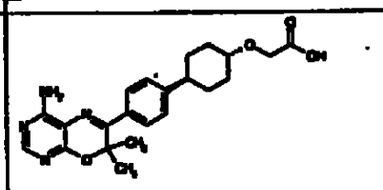
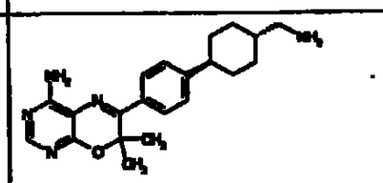
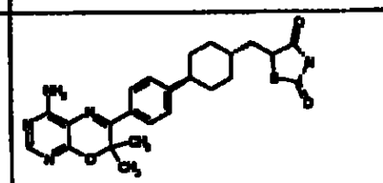
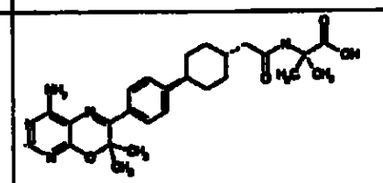
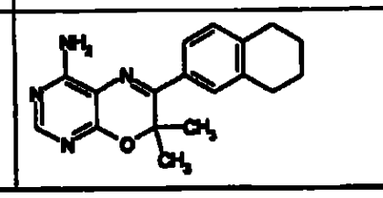
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-63		>270	1.55(s, 6H), 3.64(s, 2H), 7.04(brs, 2H), 7.39(d, 2H, J=8.0Hz), 7.69(d, 2H, J=8.0Hz), 7.76(d, 2H, J=8.0Hz), 7.94(d, 2H, J=8.0Hz), 12.32(brs, 1H)	DMSO-d6, 300
2-64		267(dec.)	1.12(s, 3H), 1.32(s, 3H), 3.63(s, 2H), 4.22(brs, 1H), 5.35(brs, 1H), 6.27(brs, 2H), 7.39(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.68(d, 2H, J=8.0Hz), 7.84(s, 1H), 7.70(d, 2H, J=8.0Hz)	DMSO-d6, 300
2-65		>250	1.48(s, 6H), 1.60(s, 6H), 6.86(brs, 2H), 7.40(d, 2H, J=8.4 Hz), 7.89(d, 2H, J=8.4 Hz), 7.98(s, 1H), 12.4(brs, 1H).	DMSO-d6, 300MHz
2-66				
2-67				
2-68		251 - 252	1.01-1.13(m, 2H), 1.39-1.53(m, 3H), 1.60(s, 6H), 1.82-1.91(m, 4H), 2.53-2.57(m, 1H), 2.83(t, 2H, J=6.0Hz), 2.89(s, 3H), 6.94(brs, 2H), 7.01(s, 1H, J=8.0Hz), 7.32(d, 2H, J=8.0Hz), 7.69(d, 2H, J=8.0Hz), 7.85(s, 1H)	DMSO-d6, 300
2-69		>250	1.04-1.12(m, 2H), 1.43-1.59(m, 3H), 1.60(s, 6H), 1.77-1.83(m, 4H), 2.38(d, 2H, J=6.9 Hz), 2.48(m, 1H), 5.24(s, 1H), 6.86(brs, 2H), 7.29(d, 2H, J=8.3 Hz), 7.62(d, 2H, J=8.3 Hz), 7.94(s, 1H), 9.20(brs, 1H), 11.20(brs, 1H).	DMSO-d6, 400MHz

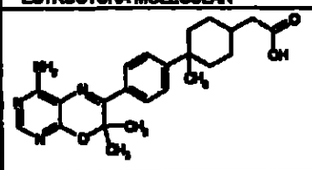
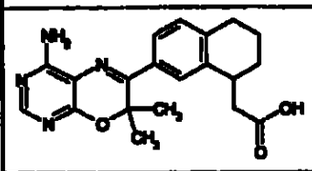
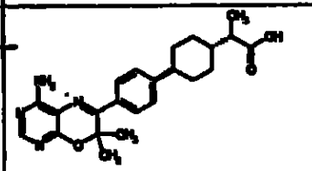
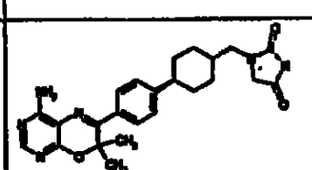
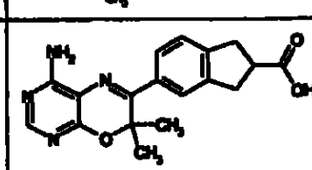
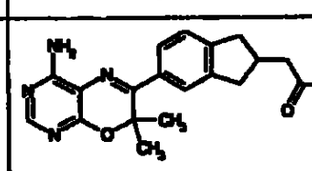
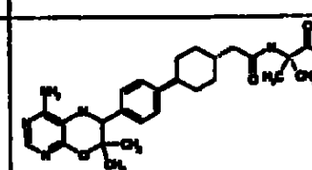
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-60		173 - 175	a mixture of keto- and enol-form; 1.04-1.12(m, 2H), 1.43-1.60(m, 2H), 1.60(s, 6H), 1.70(m,1H), 1.81-1.86(m, 4H), 2.33(d, 1H, J=8.9 Hz) and 2.37(d, 1H, J=8.9 Hz), 2.60(m, 1H), 3.65(s, 1H) and 6.00(s, 0.6H), 6.88(brs, 2H), 7.29(d, 2H, J=8.3 Hz), 7.84(d, 2H, J=8.3 Hz), 7.95(s, 1H), 12.40(brs, 0.6H).	DMSO-d6, 400MHz
2-61		159 - 162	0.97-1.13(m, 2H), 1.35-1.52(m, 3H), 1.60(s, 6H), 1.75-1.87(m, 4H), 2.48-2.59(m, 1H), 2.91(t, 2H, J=6.0Hz), 5.02(s, 2H), 6.94(br, 2H), 7.23-7.40(m, 6H), 7.84(d, 2H, J=7.7Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-62		>230	1.35-1.40(m, 2H), 1.45-1.58(m, 2H), 1.60(s, 6H), 1.83(brd, 2H, J=12.6 Hz), 2.11(brd, 2H, J=9.6 Hz), 2.52(m, 1H), 3.35(m, 1H), 4.08(s, 2H), 6.85(brs, 2H), 7.29(d, 2H, J=8.3 Hz), 7.83(d, 2H, J=8.3 Hz), 7.94(s, 1H), 12.30(brs, 1H).	DMSO-d6, 400MHz
2-63			0.99-1.08(m, 2H), 1.24-1.34(m, 1H), 1.39-1.51(m, 2H), 1.60(s, 6H), 1.76-1.92(m, 4H), 2.44(d, 2H, J=6.6Hz), 2.47-2.55(m, 1H), 6.88(br, 2H), 7.30(d, 2H, J=8.2Hz), 7.83(d, 2H, J=8.2Hz), 7.95(s, 1H)	DMSO-d6, 400MHz
2-64		>230	1.04-1.20(m, 2H), 1.43-1.60(m, 2H), 1.60(s, 6H), 1.75-1.88(m, 6H), 2.03(m, 1H), 2.81(m, 1H), 4.60(m, 1H), 6.88(brs, 2H), 7.30(d, 2H, J=8.3 Hz), 7.83(d, 2H, J=8.3 Hz), 7.94(s, 1H), 12.02(brs, 1H).	DMSO-d6, 400MHz
2-65		243 - 244	1.05-1.14(m, 2H), 1.33(s, 6H), 1.38-1.51(m, 2H), 1.60(s, 6H), 1.76-1.88(m, 6H), 2.00(d, 2H, J=6.0Hz), 2.54-2.58(m, 1H), 6.94(brs, 2H), 7.31(t, 2H, J=6.0Hz), 7.84(d, 2H, J=8.0Hz), 7.95(s, 1H), 7.98(s, 1H)	DMSO-d6, 300MHz
2-66		176-177	1.58(s, 6H), 1.72-1.77(m, 4H), 2.73-2.82(m, 4H), 6.82(br, 2H), 7.11(d, 1H, J=7.7Hz), 7.40(d, 1H, J=7.7Hz), 7.39(s, 1H), 7.95(s, 1H)	DMSO-d6, 300MHz

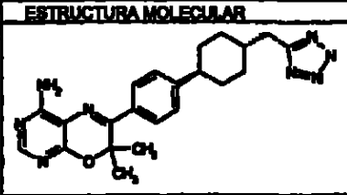
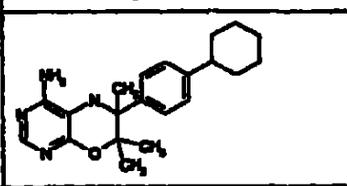
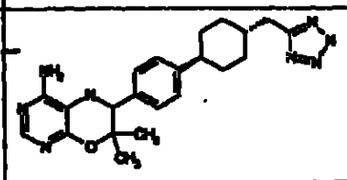
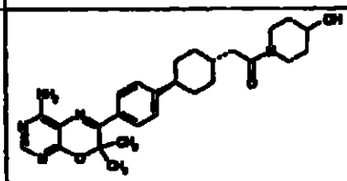
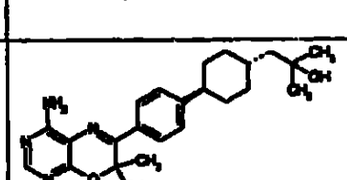
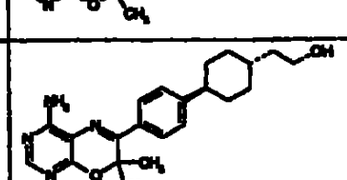
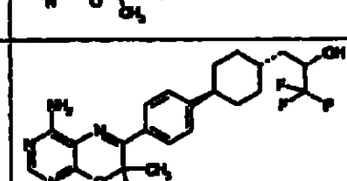
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-67		>250	0.80-0.96(m, 2H), 1.11(s, 3H), 1.41-1.65(m, 4H), 1.62(s, 6H), 1.65-1.76(m, 1H), 1.98(d, 2H, J=7.0Hz), 2.31-2.41(m, 2H), 6.55(br, 2H), 7.44(d, 2H, J=8.4Hz), 7.70(d, 2H, J=8.4Hz), 7.95(s, 1H), 11.89(brs, 1H)	DMSO-d6, 300MHz
2-68		>250	1.55-1.80(m, 6H), 1.59(s, 6H), 2.40-2.62(m, 2H), 2.68-2.82(m, 2H), 6.53(br, 2H), 7.13(d, 1H, J=7.7Hz), 7.44(d, 1H, J=7.7Hz), 7.59(s, 1H), 7.66(s, 1H), 12.15(brs, 1H)	DMSO-d6, 300MHz
2-69		>250	1.09(d, 3H, J=7.1Hz), 1.11-1.28(m, 2H); 1.43-1.52(m, 2H), 1.55-1.65(m, 1H), 1.61(s, 6H), 1.71-1.91(m, 4H), 2.15-2.23(m, 1H), 2.49-2.66(m, 1H), 6.52(br, 2H), 7.31(d, 2H, J=8.1Hz), 7.64(d, 2H, J=8.1Hz), 7.66(s, 1H), 11.97(brs, 1H)	DMSO-d6, 400MHz
2-70		212 - 214	1.04-1.30(m, 2H), 1.43-1.50(m, 2H), 1.60(s, 6H), 1.61(m, 1H), 1.75-1.88(m, 4H), 2.61(m, 1H), 3.11(d, 2H, J=7.2 Hz), 3.66(s, 2H), 6.60(brs, 2H), 7.28(d, 2H, J=8.3 Hz), 7.64(d, 2H, J=8.3 Hz), 7.94(s, 1H), 10.69(brs, 1H).	DMSO-d6, 400MHz
2-71		>250	1.58(s, 6H), 3.10-3.31(m, 4H), 3.28-3.34(m, 1H), 6.04(br, 2H), 7.28(d, 1H, J=7.7Hz), 7.48(d, 1H, J=7.7Hz), 7.58(s, 1H), 12.39(brs, 1H)	DMSO-d6, 300MHz
2-72		>250	1.58(s, 6H), 2.42(d, 2H, J=7.3Hz), 2.57-2.80(m, 3H), 3.04-3.16(m, 2H), 6.62(br, 2H), 7.28(d, 1H, J=8.1Hz), 7.46(d, 1H, J=8.1Hz), 7.53(s, 1H), 7.69(s, 1H), 12.06(brs, 1H)	DMSO-d6, 300MHz
2-73		>250	1.03-1.13(m, 2H), 1.09(s, 3H), 1.22(s, 3H), 1.32(s, 6H), 1.35-1.48(m, 2H), 1.57-1.85(m, 6H), 1.99(d, 2H, J=6.6Hz), 2.43-2.50(m, 1H), 4.11(s, 1H), 5.25(s, 1H), 6.50(br, 2H), 7.24(d, 2H, J=8.1Hz), 7.35(d, 2H, J=8.1Hz), 7.51(s, 1H), 7.94(s, 1H), 11.93(brs, 1H)	DMSO-d6, 400MHz

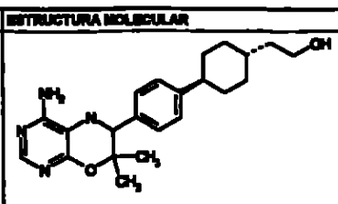
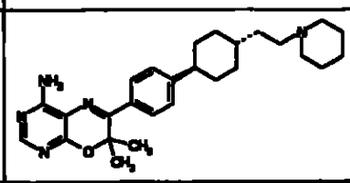
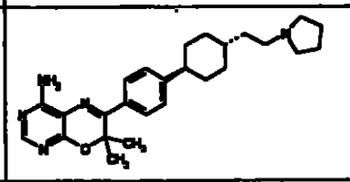
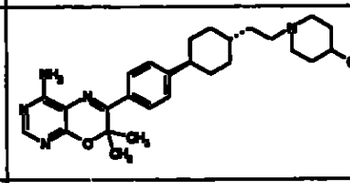
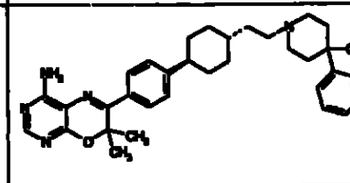
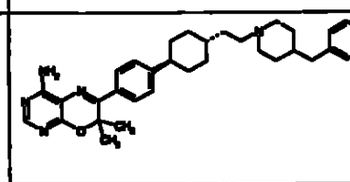
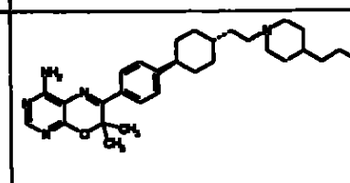
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-74		>250	1.11-1.27(m, 2H), 1.39-1.54(m, 2H), 1.60(s, 6H), 1.59-1.67(m, 6H), 2.50-2.61(m, 1H), 2.63(d, 2H, J=7.0Hz), 6.93(br, 2H), 7.20(d, 2H, J=8.4Hz), 7.64(d, 2H, J=8.4Hz), 7.85(s, 1H)	DMSO-d6, 300MHz
2-75		244 - 245	1.03(s, 3H), 1.26(s, 3H), 1.33-1.43(m, 4H), 1.46(s, 3H), 1.65-1.80(m, 6H), 2.53-2.55(m, 1H), 5.15(s, 1H), 6.23(bra, 2H), 7.23(d, 2H, J=8.0Hz), 7.53(d, 2H, J=8.0Hz), 7.81(s, 1H)	DMSO-d6, 300MHz
2-76		>250	1.11-1.27(m, 2H), 1.36-1.51(m, 2H), 1.58-1.67(m, 8H), 2.41-2.52(m, 1H), 2.53(d, 2H, J=6.6Hz), 4.11(s, 1H), 5.26(s, 1H), 6.20(br, 2H), 7.23(d, 2H, J=8.1Hz), 7.35(d, 2H, J=8.1Hz), 7.81(s, 1H), 15.99(bra, 1H)	DMSO-d6, 400MHz
2-77		137 - 139	1.04-1.34(m, 4H), 1.43-1.80(m, 2H), 1.60(s, 6H), 1.63-1.86(m, 7H), 2.23(d, 2H, J=7.2 Hz), 2.61(m, 1H), 3.00(m, 1H), 3.18(m, 1H), 3.65-3.76(m, 2H), 3.84(m, 1H), 4.85(bra, 1H), 6.86(bra, 2H), 7.30(d, 2H, J=8.3 Hz), 7.63(d, 2H, J=8.3 Hz), 7.94(s, 1H).	DMSO-d6, 400MHz
2-78		185 - 187	1.04-1.20(m, 2H), 1.12(s, 6H), 1.21(d, 2H, J=6.4 Hz), 1.43-1.53(m, 3H), 1.60(s, 6H), 1.75-1.96(m, 4H), 2.51(m, 1H), 4.01(s, 1H), 6.86(bra, 2H), 7.29(d, 2H, J=8.3 Hz), 7.63(d, 2H, J=8.3 Hz), 7.94(s, 1H).	DMSO-d6, 400MHz
2-79		207 - 208	1.09-1.14(m, 2H), 1.34-1.51(m, 6H), 1.60-1.91(m, 4H), 2.53-2.57(m, 1H), 3.43-3.49(m, 2H), 4.27(bra, 1H), 6.82(bra, 2H), 7.30(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.85(s, 1H)	DMSO-d6, 300
2-80		271 - 272	0.88-1.34(m, 2H), 1.33-1.84(m, 10H), 1.76-1.98(m, 6H), 2.52-2.59(m, 1H), 3.98-4.03(m, 1H), 6.04(bra, 1H), 6.91(bra, 2H), 7.31(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.85(s, 1H)	DMSO-d6, 400

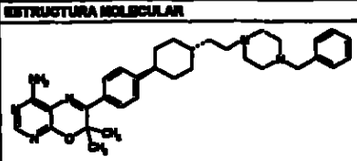
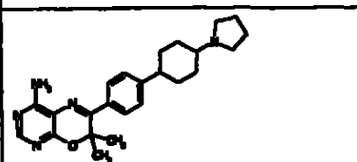
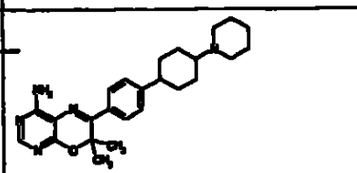
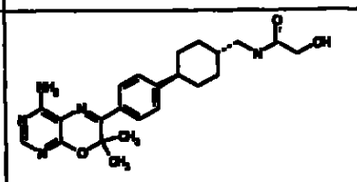
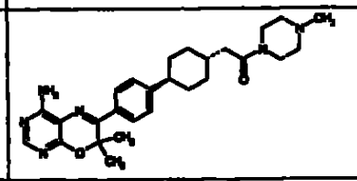
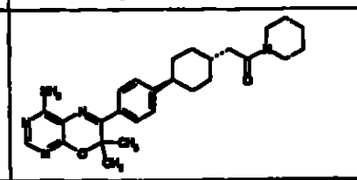
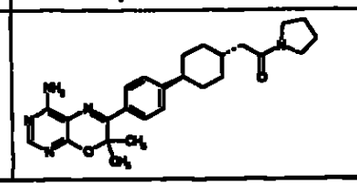
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	RMN(δ)	SOLVENTE
2-81			1.00-1.11(m, 6H), 1.22(s, 3H), 1.33-1.49(m, 6H), 1.76-1.85(m, 4H), 2.41-2.49(m, 1H), 3.43-3.49(m, 2H), 4.11(brs, 1H), 4.28-4.33(m, 1H), 5.25(brs, 1H), 6.22(brs, 2H), 7.24(d, 2H, J=8.0Hz), 7.38(d, 2H, J=8.0Hz), 7.82(s, 1H)	DMSO-d6, 300
2-82		209 - 210	1.08-1.17(m, 2H), 1.32-1.52(m, 6H), 1.58-1.90(m, 11H), 1.81(s, 6H), 2.54-2.63(m, 1H), 2.77-2.89(m, 2H), 2.99-3.10(m, 2H), 7.03(brs, 2H), 7.31(d, 2H, J=8.0Hz), 7.85(d, 2H, J=8.0Hz), 7.96(s, 1H)	DMSO-d6, 300MHz
2-83		142 - 143	1.04-1.16(m, 2H), 1.37-1.54(m, 6H), 1.80(brs, 6H), 1.78-2.02(m, 6H), 2.54-2.60(m, 1H), 2.81-3.03(m, 2H), 3.07-3.22(m, 2H), 7.03(brs, 2H), 7.31(d, 2H, J=8.0Hz), 7.86(d, 2H, J=8.0Hz), 7.96(brs, 1H)	DMSO-d6, 300MHz
2-84		217 - 218	1.02-1.14(m, 2H), 1.33-1.49(m, 10H), 1.80(s, 6H), 1.89-1.98(m, 6H), 2.54-2.58(m, 1H), 2.71-2.81(m, 2H), 3.42-3.52(m, 1H), 4.56(brs, 1H), 6.93(brs, 2H), . 7.30(d, 2H, J=8.0Hz), 7.84(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-85		115 - 116	1.04-1.18(m, 2H), 1.34-1.51(m, 6H), 1.58-1.88(m, 2H), 1.80(s, 6H), 1.90-1.98(m, 7H), 2.36-2.49(m, 2H), 2.51-2.60(m, 1H), 2.68-2.80(m, 2H), 4.80(brs, 1H), 6.92(brs, 2H), 7.18-7.34(m, 5H), 7.48(d, 2H, J=8.0Hz), 7.85(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-86		190 - 191	1.01-1.23(m, 4H), 1.30-1.57(m, 7H), 1.80(s, 6H), 1.74-1.88(m, 7H), 2.25-2.31(m, 2H), 2.53-2.57(m, 1H), 2.80-2.88(m, 2H), 3.30(s, 2H), 6.91(brs, 2H), 7.14-7.30(m, 7H), 7.84(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-87		221 - 222	1.02-1.14(m, 4H), 1.31-1.54(m, 9H), 1.80(s, 6H), 1.78-1.87(m, 7H), 2.27-2.37(m, 2H), 2.54-2.57(m, 1H), 2.80-2.90(m, 2H), 3.40-3.46(m, 2H), 4.29(t, 1H, J=4.5Hz), 6.93(brs, 2H), 7.30(d, 2H, J=8.0Hz), 7.84(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz

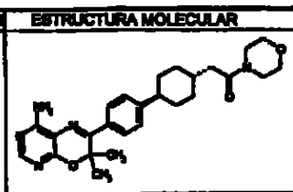
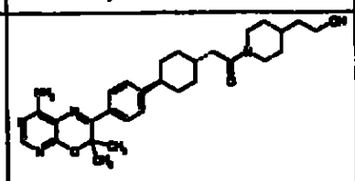
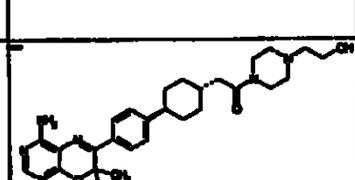
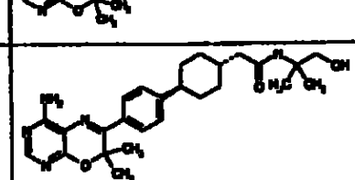
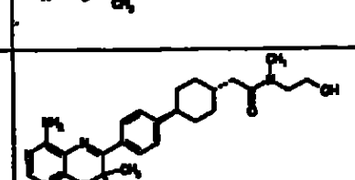
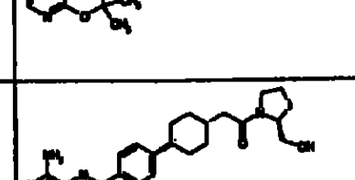
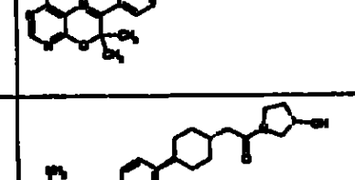
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	RMN(δ)	SOLVENTE
2-88		176 - 178	1.08-1.13(m, 2H), 1.34-1.50(m, 6H), 1.60(s, 6H), 1.78-1.85(m, 6H), 2.31-2.45(m, 6H), 2.53-2.57(m, 1H), 3.46(s, 2H), 6.82(brs, 2H), 7.24-7.35(m, 7H), 7.84(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-89			1.47-1.57(m, 6H), 1.70(s, 6H), 1.74-1.86(m, 3H), 1.88-2.07(m, 4H), 2.17-2.27(m, 1H), 2.44-2.61(m, 3H), 2.64-2.74(m, 1H), 6.40(br, 2H), 7.34(br, 2H), 7.68(br, 2H), 8.14(s, 1H)	CDCl3, 400MHz
2-90			1.34-1.85(m, 10H), 1.81(s, 6H), 1.81-1.88(m, 6H), 2.14-2.27(m, 1H), 2.31-2.45(m, 3H), 2.88-2.83(m, 1H), 6.90(br, 2H), 7.31(br, 2H), 7.65(br, 2H), 7.96(s, 1H)	DMSO-d6, 400MHz
2-91			1.04-1.13(m, 2H), 1.38-1.55(m, 3H), 1.60(s, 6H), 1.75-1.85(m, 3H), 2.51(m, 1H), 3.01(brt, 2H, J=6.4 Hz), 3.80(d, 2H, J=5.6 Hz), 5.41(brt, 1H, J=5.6 Hz), 6.90(brs, 2H), 7.28(d, 2H, J=8.3 Hz), 7.62(d, 2H, J=8.3 Hz), 7.89(brt, 1H, J=6.4 Hz), 7.93(s, 1H).	DMSO-d6, 400MHz
2-92		113 - 115	1.04-1.17(m, 2H), 1.43-1.60(m, 2H), 1.60(s, 6H), 1.80-1.84(m, 6H), 2.19(s, 3H), 2.23-2.31(m, 4H), 2.51(m, 1H), 3.43-3.48(m, 4H), 6.91(brs, 2H), 7.30(d, 2H, J=8.3 Hz), 7.63(d, 2H, J=8.3 Hz), 7.95(s, 1H).	DMSO-d6, 300MHz
2-93		146 - 147	1.03-1.20(m, 2H), 1.37-1.86(m, 16H), 2.22(d, 2H, J=6.0Hz), 2.53-2.55(m, 1H), 3.39-3.46(m, 4H), 6.92(brs, 2H), 7.31(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-94		232 - 233	1.08-1.19(m, 2H), 1.41-1.63(m, 8H), 1.71-1.91(m, 9H), 2.19(d, 2H, J=6.0Hz), 2.51-2.59(m, 1H), 3.28-3.31(m, 2H), 3.41(t, 2H, J=8.0Hz), 6.92(brs, 2H), 7.31(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300

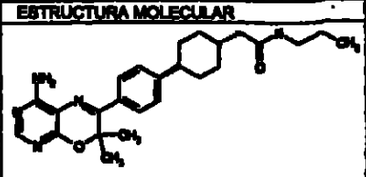
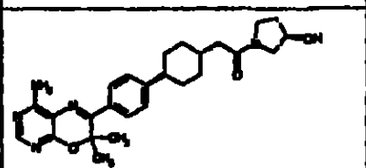
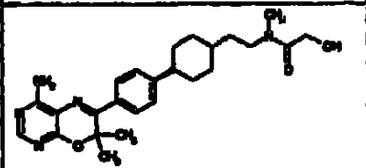
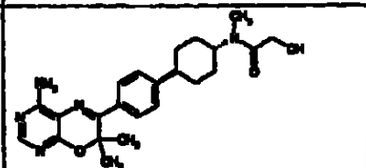
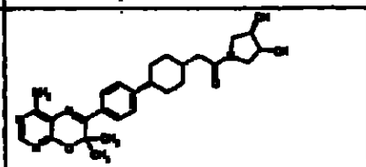
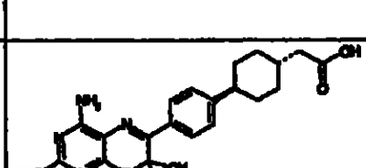
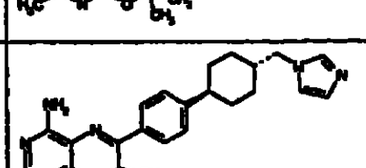
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-96		199 - 200	1.09-1.21(m, 2H), 1.41-1.66(m, 2H), 1.80(s, 6H), 1.74-1.87(m, 4H), 2.23(d, 2H, J=6.0Hz), 3.41-3.58(m, 16H), 6.93(m, 2H), 7.31(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-98		112 - 113	0.89-1.18(m, 4H), 1.22-1.55(m, 4H), 1.80(s, 6H), 1.87-1.93(m, 7H), 2.23(d, 2H, J=6.0Hz), 2.52-2.67(m, 1H), 2.83-3.02(m, 2H), 3.41-3.47(m, 2H), 3.84-3.93(m, 2H), 4.33-4.42(m, 2H), 6.93(m, 2H), 7.31(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-97		225 - 226	1.09-1.18(m, 2H), 1.41-1.53(m, 2H), 1.80(s, 6H), 1.74-1.89(m, 8H), 2.23(d, 2H, J=6.0Hz), 2.33-2.43(m, 6H), 2.83-2.89(m, 1H), 3.43-3.54(m, 6H), 4.41(t, 1H, J=6.0Hz), 6.93(m, 2H), 7.31(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-99		131 - 133	1.04-1.12(m, 2H), 1.18(s, 6H), 1.33-1.55(m, 2H), 1.80(s, 6H), 1.85-1.89(m, 6H), 1.97(d, 2H, J=6.9 Hz), 2.61(m, 1H), 3.36(d, 2H, J=6.9 Hz), 4.89(t, 1H, J=6.9 Hz), 6.92(m, 2H), 7.64(s, 2H), 7.27(d, 2H, J=8.3 Hz), 7.61(d, 2H, J=8.3 Hz), 7.92(s, 1H).	DMSO-d6, 400MHz
2-99		113 - 115	a mixture of 2 conformers: 1.04-1.12(m, 2H), 1.38-1.55(m, 2H), 1.80(s, 6H), 1.88-1.93(m, 6H), 2.20-2.28(m, 2H), 2.61(m, 1H), 2.82 and 3.01(s, 2H), 3.30-3.51(m, 4H), 4.80 and 4.77(brt, 1H, J=6.6 Hz), 6.92(m, 2H), 7.29(d, 2H, J=8.3 Hz), 7.62(d, 2H, J=8.3 Hz), 7.92(s, 1H).	DMSO-d6, 400MHz
2-100		184 - 185	1.03-1.21(m, 2H), 1.38-1.55(m, 2H), 1.82(s, 6H), 1.71-1.95(m, 6H), 2.13-2.39(m, 2H), 2.43-2.58(m, 1H), 3.33-3.53(m, 4H), 3.85-4.02(m, 1H), 4.57-4.82(m, 1H), 6.91(br, 2H), 7.31(d, 2H, J=8.4Hz), 7.64(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-101		227 - 229	1.03-1.20(m, 2H), 1.37-1.57(m, 2H), 1.80(s, 6H), 1.89-1.95(m, 7H), 2.09-2.30(m, 2H), 2.44-2.58(m, 1H), 3.33-3.54(m, 2H), 4.20-4.39(m, 2H), 4.80-5.00(m, 1H), 6.92(br, 2H), 7.31(d, 2H, J=8.4Hz), 7.64(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz

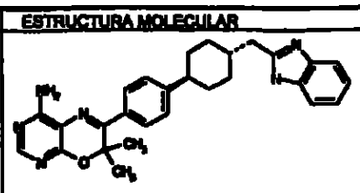
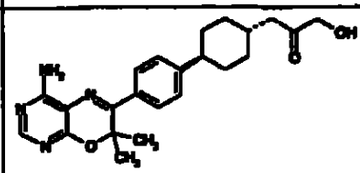
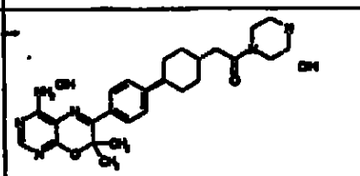
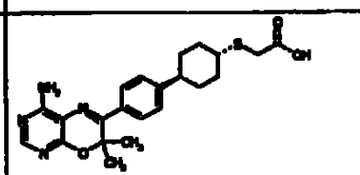
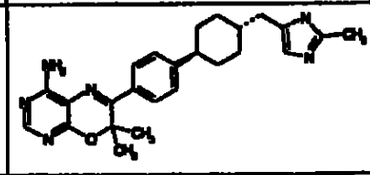
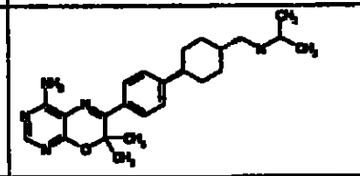
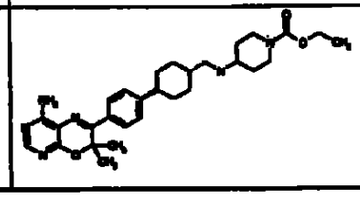
z 86

Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-102		214 - 215	0.84(t, 3H, J=7.2Hz), 1.02-1.19(m, 2H), 1.24-1.53(m, 4H), 1.65(s, 6H), 1.59-1.86(m, 6H), 1.89(d, 2H, J=6.6Hz), 2.48-2.57(m, 1H), 3.00(q, 2H, J=6.6Hz), 6.53(br, 2H), 7.30(d, 2H, J=8.4Hz), 7.64(d, 2H, J=8.4Hz), 7.74(t, 1H, J=5.6Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-103		231 - 232	1.02-1.22(m, 2H), 1.38-1.57(m, 2H), 1.60(s, 6H), 1.69-1.87(m, 6H), 2.08-2.21(m, 2H), 2.47-2.58(m, 1H), 3.29-3.58(m, 4H), 4.16-4.41(m, 2H), 4.81-5.00(m, 1H), 6.69(br, 2H), 7.31(d, 2H, J=8.4Hz), 7.64(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-104		186 - 188	1.08-1.55(m, 7H), 1.60(s, 6H), 1.76-1.94(m, 4H), 2.48-2.61(m, 1H), 2.85(s, 3H), 4.05(s, 1.4H), 4.09(s, 0.6H), 6.62(br, 2H), 7.30(d, 2H, J=8.1Hz), 7.64(d, 2H, J=8.1Hz), 7.96(s, 1H)	DMSO-d6, 300MHz
2-105		>250	1.53-1.92(m, 6H), 1.61(s, 6H), 2.49-2.63(m, 1H), 2.76(s, 1.5H), 2.79(s, 1.5H), 4.09(s, 0.5H), 4.16(s, 0.5H), 4.35-4.47(m, 1H), 6.63(br, 2H), 7.33(m, 2H, J=8.2Hz), 7.66(d, 2H, J=8.2Hz), 7.96(s, 1H)	DMSO-d6, 300MHz
2-106		250 - 252	1.03-1.22(m, 2H), 1.38-1.58(m, 2H), 1.60(s, 6H), 1.69-1.82(m, 6H), 2.12(d, 2H, J=6.6Hz), 2.45-2.59(m, 1H), 3.16-3.41(m, 3H), 3.68-3.80(m, 1H), 3.84-4.09(m, 2H), 4.84(br, 1H), 4.92(br, 1H), 6.63(br, 2H), 7.31(d, 2H, J=8.1Hz), 7.64(d, 2H, J=8.1Hz), 7.96(s, 1H)	DMSO-d6, 300MHz
2-107		>250	1.07-1.18(m, 2H), 1.41-1.53(m, 2H), 1.59(s, 6H), 1.71-1.85(m, 6H), 2.15(d, 2H, J=4.0Hz), 2.24(s, 3H), 2.51-2.57(m, 1H), 6.64(bs, 2H), 7.29(d, 2H, J=8.0Hz), 7.61(d, 2H, J=8.0Hz), 12.04(bro, 1H)	DMSO-d6, 400MHz
2-108		202 - 203	1.08-1.18(m, 2H), 1.38-1.48(m, 2H), 1.59-1.84(m, 6H), 1.59(s, 6H), 2.51-2.55(m, 1H), 3.65(d, 2H, J=6.0Hz), 6.89-7.15(m, 1H), 6.91(bro, 2H), 7.27(d, 2H, J=8.0Hz), 7.62(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz

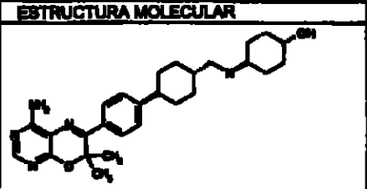
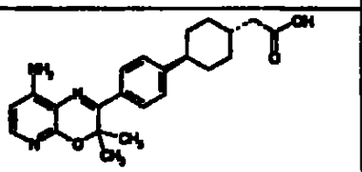
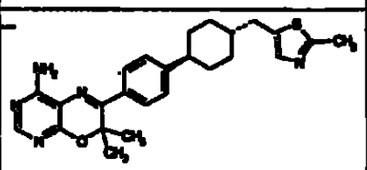
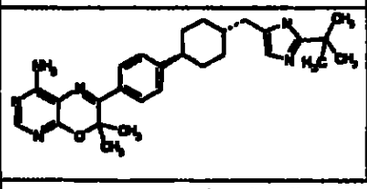
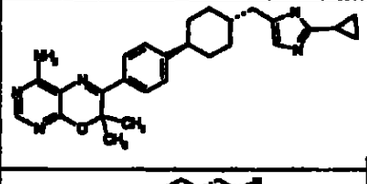
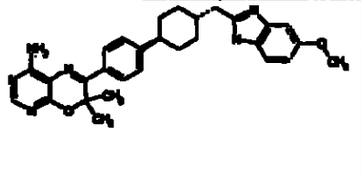
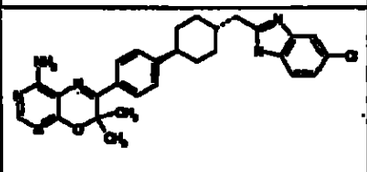
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• **Tabla 2 (Continuación)**

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-109		>230	1.18-1.35(m, 2H), 1.37-1.58(m, 3H), 1.60(s, 6H), 1.80-1.96(m, 6H), 2.51(m, 1H), 2.75(d, 2H, J=8.3 Hz), 6.91(bm, 2H), 7.03-7.22(m, 2H), 7.30(d, 2H, J=8.3 Hz), 7.28-7.57(m, 2H), 7.63(d, 2H, J=8.3 Hz), 7.95(s, 1H), 12.19(bm, 1H).	DMSO-d6, 400MHz
2-110		185 - 186	1.01-1.19(m, 2H), 1.35-1.59(m, 2H), 1.60(s, 6H), 1.72-1.86(m, 5H), 2.34(d, 2H, J=6.0Hz), 2.84-2.89(m, 1H), 4.05(d, 2H, J=6.0Hz), 5.04(t, 1H, J=6.0Hz), 6.81(bm, 2H), 7.31(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.86(s, 1H)	DMSO-d6, 300MHz
2-111		>250	1.04-1.21(m, 2H), 1.36-1.58(m, 2H), 1.58(s, 6H), 1.70-1.89(m, 5H), 2.28(d, 2H, J=6.4Hz), 2.48-2.68(m, 1H), 2.98-3.13(m, 4H), 3.60-3.77(m, 4H), 7.32(d, 2H, J=8.3Hz), 7.65(br, 2H), 7.68(d, 2H, J=8.3Hz), 8.16(s, 1H), 9.32(br, 2H)	DMSO-d6, 300MHz
2-112		>250	1.31-1.58(m, 4H), 1.60(s, 6H), 1.83-1.91(m, 2H), 2.09-2.16(m, 2H), 2.53-2.65(m, 1H), 2.77-2.86(m, 1H), 3.30(s, 2H), 6.93(bm, 2H), 7.31(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.94(s, 1H), 12.40(bm, 1H)	DMSO-d6, 300
2-113		172 - 173	1.04-1.13(m, 2H), 1.34-1.48(m, 2H), 1.58(s, 6H), 1.78-1.84(m, 5H), 2.23(s, 3H), 2.38(d, 2H, J=6.0Hz), 2.51-2.58(m, 1H), 6.88(s, 1H), 6.92(bm, 2H), 7.28(d, 2H, J=8.0Hz), 7.63(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-114		250	1.04-1.22(m, 2H), 1.10(d, 6H, J=6.1Hz), 1.38-1.58(m, 4H), 1.60(s, 6H), 1.80-1.97(m, 5H), 2.49-2.62(m, 1H), 2.63-2.70(m, 1H), 6.93(br, 2H), 7.31(d, 2H, J=8.4Hz), 7.65(d, 2H, J=8.4Hz), 7.93(s, 1H)	DMSO-d6, 300MHz
2-115		127 - 128	0.99-1.23(m, 6H), 1.17(t, 3H, J=7.1Hz), 1.38-1.62(m, 2H), 1.60(s, 6H), 1.72-1.94(m, 6H), 2.48-2.58(m, 1H), 2.79-2.94(m, 2H), 3.81-3.89(m, 2H), 4.02(q, 2H, J=7.1Hz), 6.93(br, 2H), 7.30(d, 2H, J=8.4Hz), 7.64(d, 2H, J=8.4Hz), 7.89(s, 1H)	DMSO-d6, 300MHz

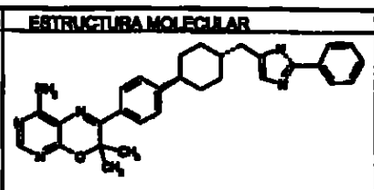
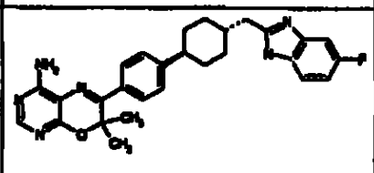
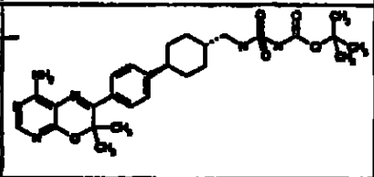
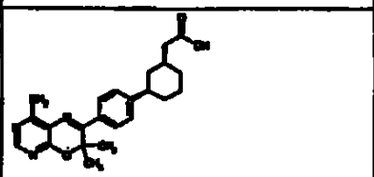
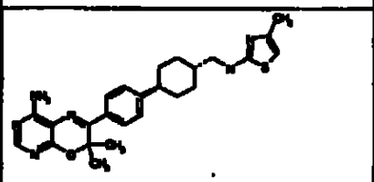
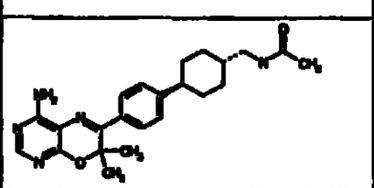
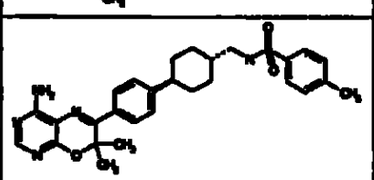
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-116		>250	0.93-1.32(m, 6H), 1.33-1.55(m, 4H), 1.60(s, 6H), 1.74-1.95(m, 7H), 2.30-2.34(m, 1H), 2.41(d, 2H, J=6.4Hz), 2.47-2.55(m, 1H), 3.27-3.39(m, 1H), 4.44(d, 1H, J=4.8Hz), 6.98(br, 2H), 7.28(d, 2H, J=8.3Hz), 7.63(d, 2H, J=8.3Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-117		>250	1.07-1.19(m, 2H), 1.43-1.53(m, 2H), 1.55(s, 6H), 1.70-1.85(m, 5H), 2.19(d, 2H, J=6.0Hz), 2.51-2.55(m, 1H), 6.21(bs, 2H), 6.31(d, 1H, J=8.0Hz), 7.25(d, 2H, J=8.0Hz), 7.40(d, 1H, J=8.0Hz), 7.60(d, 2H, J=8.0Hz), 11.94(bs, 1H)	DMSO-d6, 400MHz
2-118		215 - 216	1.08-1.23(m, 2H), 1.38-1.50(m, 2H), 1.59(s, 6H), 1.68-1.83(m, 5H), 2.52-2.55(m, 1H), 2.58(d, 2H, J=4.0Hz), 2.62(s, 3H), 6.56(bm, 2H), 7.09(s, 1H), 7.28(d, 2H, J=8.0Hz), 7.62(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-119		>250	1.08-1.18(m, 2H), 1.26(s, 6H), 1.36-1.48(m, 2H), 1.60(s, 6H), 1.75-1.85(m, 5H), 2.38(d, 2H, J=4.0Hz), 2.52-2.56(m, 1H), 6.56(bm, 1H), 6.94(bm, 2H), 7.28(d, 2H, J=12.0Hz), 7.62(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-120		226 - 227	0.88-1.18(m, 7H), 1.38-1.54(m, 2H), 1.59(s, 6H), 1.74-1.88(m, 5H), 2.33(d, 2H, J=4.0Hz), 2.53-2.56(m, 1H), 6.60(s, 1H), 6.94(bm, 2H), 7.28(d, 2H, J=8.0Hz), 7.62(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-121			1.14-1.34(m, 2H), 1.37-1.55(m, 2H), 1.60(s, 6H), 1.80-1.95(m, 5H), 2.51(m, 1H), 2.71(d, 2H, J=6.3 Hz), 3.77(s, 3H), 6.74(dd, 1H, J=2.2, 8.4 Hz), 6.91(bm, 2H), 6.99(d, 1H, J=2.2 Hz), 7.30(d, 2H, J=8.3 Hz), 7.35(d, 1H, J=8.4 Hz), 7.64(d, 2H, J=8.3 Hz), 7.95(s, 1H), 12.05(bm, 1H).	DMSO-d6, 300MHz
2-122		>230	1.15-1.33(m, 2H), 1.37-1.55(m, 2H), 1.60(s, 6H), 1.80-1.95(m, 5H), 2.51(m, 1H), 2.75(d, 2H, J=6.3 Hz), 6.92(bm, 2H), 7.14(d, 1H, J=8.4 Hz), 7.30(d, 2H, J=8.3 Hz), 7.39-7.53(m, 2H), 7.63(d, 2H, J=8.3 Hz), 7.95(s, 1H), 12.37(bm, 1H).	DMSO-d6, 300MHz

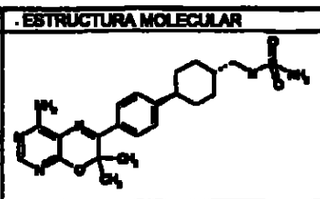
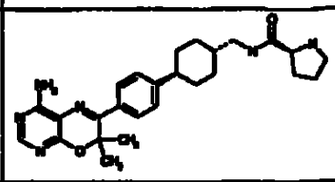
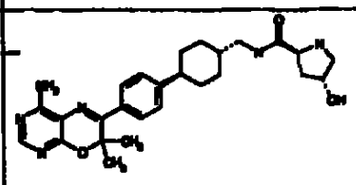
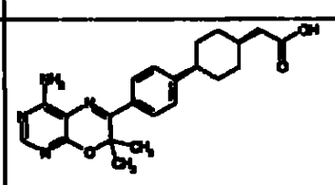
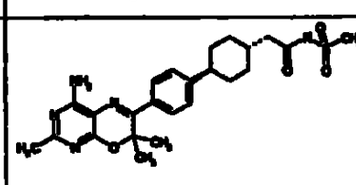
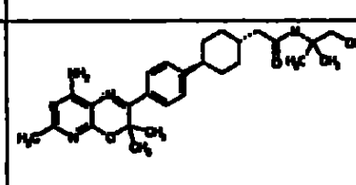
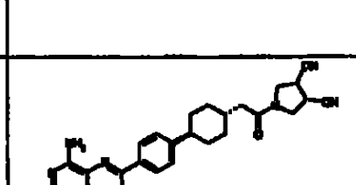
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-123		230 - 231	1.09-1.19(m, 2H), 1.41-1.52(m, 2H), 1.55(s, 6H), 1.76-1.86(m, 6H), 2.53-2.59(m, 1H), 3.18(d, 2H, J=12.0Hz), 6.71(bs, 1H), 6.83(bs, 2H), 7.27-7.42(m, 6H), 7.52(d, 2H, J=8.0Hz), 7.88(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-124		>230	1.14-1.33(m, 2H), 1.37-1.56(m, 2H), 1.60(s, 6H), 1.70-2.03(m, 5H), 2.51(m, 1H), 2.73(d, 2H, J=7.0 Hz), 6.73-7.13(m, 3H), 7.17-7.35(m, 3H), 7.44(bs, 1H), 7.62(d, 2H, J=8.3 Hz), 7.93(s, 1H), 12.30(bs, 1H).	DMSO-d6, 400MHz
2-125			0.97-1.11(m, 2H), 1.34-1.84(m, 12H), 1.60(s, 6H), 1.76-1.86(m, 4H), 2.53-2.58(m, 1H), 2.76-2.83(m, 2H), 6.94(bs, 2H), 7.30(d, 2H, J=8.0Hz), 7.57(bs, 1H), 7.86(d, 2H, J=8.0Hz), 7.93(s, 1H), 10.78(bs, 1H)	DMSO-d6, 300
2-126		234 - 235	0.93-1.50(m, 4H), 1.60(s, 6H), 1.75-1.91(m, 5H), 2.16(d, 2H, J=6.0Hz), 2.57-2.58(m, 1H), 6.95(bs, 2H), 7.29(d, 2H, J=8.0Hz), 7.84(d, 2H, J=8.0Hz), 7.98(s, 1H), 11.94(bs, 1H)	DMSO-d6, 300
2-127		228 - 230	1.03-1.17(m, 2H), 1.36-1.51(m, 2H), 1.56-1.67(m, 7H), 1.88-1.95(m, 4H), 2.09(s, 3H), 2.51-2.59(m, 1H), 3.05-3.16(m, 2H), 6.11(bs, 1H), 6.94(bs, 2H), 7.31(d, 2H, J=8.0Hz), 7.45-7.49(m, 1H), 7.86(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 300
2-128		253 - 254	0.98-1.13(m, 2H), 1.35-1.51(m, 2H), 1.60(s, 6H), 1.77-1.86(m, 7H), 2.52-2.58(m, 1H), 2.91-2.95(m, 2H), 6.93(bs, 2H), 7.30(d, 2H, J=8.0Hz), 7.52(d, 2H, J=8.0Hz), 7.52(t, 1H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 300
2-129		206 - 207	0.93-1.06(m, 2H), 1.32-1.47(m, 2H), 1.60(s, 6H), 1.76-1.86(m, 4H), 2.38(s, 3H), 2.51-2.54(m, 1H), 2.57-2.62(m, 2H), 6.93(bs, 2H), 7.29(d, 2H, J=8.0Hz), 7.41(d, 2H, J=8.0Hz), 7.54(t, 1H, J=8.0Hz), 7.84(d, 2H, J=8.0Hz), 7.89(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 300

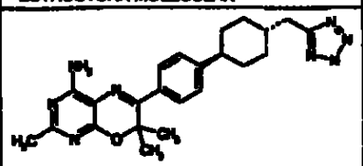
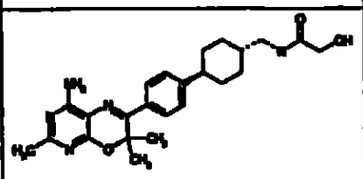
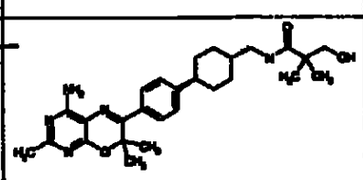
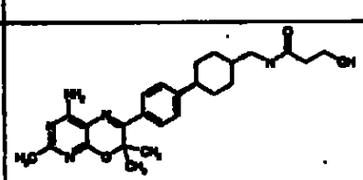
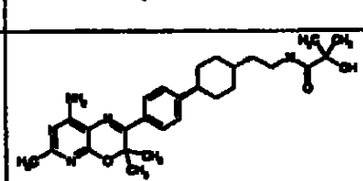
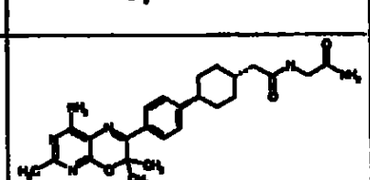
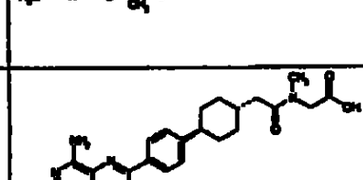
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-130		226 - 227	0.98-1.11(m, 2H), 1.27-1.55(m, 2H), 1.60(s, 6H), 1.75-1.95(m, 4H), 2.53-2.57(m, 1H), 2.74-2.79(m, 2H), 6.43(s, 2H), 6.80(d, 1H, J=8.0Hz), 6.93(brs, 2H), 7.31(d, 2H, J=8.0Hz), 7.66(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-131		230 - 231	0.99-1.13(m, 2H), 1.35-2.01(m, 10H), 2.51-2.55(m, 1H), 2.77-2.80(m, 2H), 2.95-3.01(m, 2H), 3.49-3.53(m, 1H), 6.80(brs, 2H), 7.30(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.91-7.97(m, 2H)	DMSO-d6, 300
2-132		217 - 218	0.98-1.14(m, 2H), 1.37-1.99(m, 10H), 2.53-2.55(m, 1H), 2.73-2.85(m, 2H), 2.99-3.00(m, 2H), 3.71(t, 1H, J=7.5Hz), 4.15(brs, 1H), 4.85(brs, 1H), 6.83(brs, 2H), 7.30(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.94-7.95(m, 2H)	DMSO-d6, 300
2-133		>230	1.61(s, 6H), 1.69-1.76(m, 6H), 2.19(m, 1H), 2.37(d, 2H, J=7.2 Hz), 2.60(m, 1H), 6.84(brs, 2H), 7.24(d, 2H, J=8.3 Hz), 7.64(d, 2H, J=8.3 Hz), 7.93(s, 1H).	DMSO-d6, 300MHz
2-134		226 - 228	1.07-1.18(m, 2H), 1.43-1.53(m, 2H), 1.58(s, 6H), 1.77-1.85(m, 6H), 1.91(s, 3H), 2.20(d, 2H, J=4.0Hz), 2.24(s, 3H), 2.54-2.57(m, 1H), 3.22(s, 3H), 6.81(brs, 2H), 7.28(d, 2H, J=8.0Hz), 7.61(d, 2H, J=12.0Hz), 11.66 and 11.93(brs, 1H)	DMSO-d6, 400MHz
2-135		229 - 230	1.01-1.13(m, 2H), 1.17(s, 6H), 1.41-1.51(m, 2H), 1.58(s, 6H), 1.66-1.84(m, 6H), 1.98(d, 2H, J=8.0Hz), 2.24(s, 3H), 2.52-2.55(m, 1H), 3.38(d, 2H, J=4.0Hz), 4.90(t, 1H, J=4.0Hz), 6.82(brs, 2H), 7.26(m, 1H), 7.28(d, 2H, J=8.0Hz), 7.60(d, 2H, J=8.0Hz)	DMSO-d6, 400MHz
2-136		210 - 211	1.07-1.19(m, 2H), 1.43-1.52(m, 2H), 1.58(s, 6H), 1.76-1.86(m, 6H), 2.12(d, 2H, J=8.0Hz), 2.24(s, 3H), 2.51-2.55(m, 1H), 3.15-3.28(m, 2H), 3.35-3.39(m, 1H), 3.84-3.88(m, 1H), 3.98-4.06(m, 2H), 4.87(d, 1H, J=4.0Hz), 4.95(d, 1H, J=4.0Hz), 6.80(brs, 2H), 7.28(d, 2H, J=8.0Hz), 7.60(d, 2H, J=8.0Hz)	DMSO-d6, 400MHz

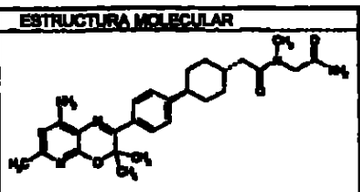
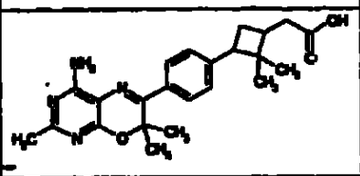
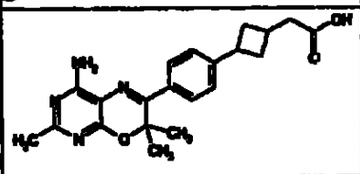
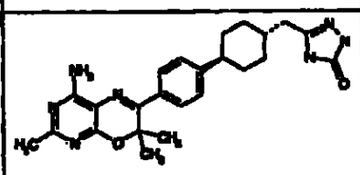
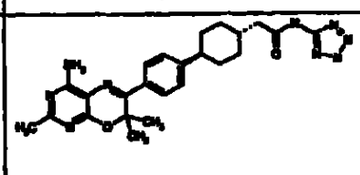
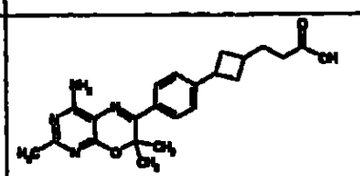
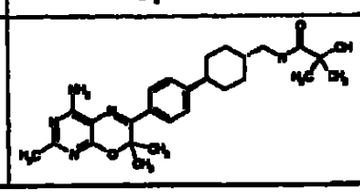
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-137		>260	1.13-1.24(m, 2H), 1.38-1.50(m, 2H), 1.57(s, 6H), 1.73-1.83(m, 6H), 2.34(s, 3H), 2.82(d, 2H, J=6.0Hz), 3.25-3.39(m, 1H), 6.81(bra, 2H), 7.27(d, 2H, J=8.0Hz), 7.60(d, 2H, J=8.0Hz)	DMSO-d6, 400MHz
2-138		236 - 239	0.99-1.15(m, 2H), 1.38-1.55(m, 3H), 1.58(s, 6H), 1.75-1.89(m, 4H), 2.24(s, 3H), 2.47-2.61(m, 1H), 3.01(t, 2H, J=6.0Hz), 3.80(d, 2H, J=6.0Hz), 8.42(t, 1H, J=6.0Hz), 6.82(br, 2H), 7.26(d, 2H, J=8.3Hz), 7.61(d, 2H, J=8.3Hz), 7.88(t, 1H, J=6.0Hz)	DMSO-d6, 300MHz
2-139		249 - 250	1.03(s, 6H), 1.08-1.08(m, 2H), 1.39-1.48(m, 3H), 1.58(s, 6H), 1.81(m, 4H), 2.23(s, 3H),2.68(m, 2H), 3.27(d, 2H, J=6.3Hz), 4.86(t, 1H, J=5.3Hz),6.80(bra, 2H), 7.25(d, 2H, J=8.3Hz), 7.44(t, 1H, J=6.6Hz), 7.62(d, 2H, J=8.3Hz).	DMSO-d6, 300MHz
2-140		223 - 224	0.99-1.10(m, 2H), 1.37-1.48(m, 2H), 1.58(s, 6H), 1.82(m, 4H), 2.23(s, 3H), 2.25(t, 2H, J=6.9Hz), 2.66(m, 2H), 3.61(dt, 1H, J=6.6Hz, 6.3Hz), 4.59(t, 1H, J=5.3Hz), 6.80(bra, 2H), 7.29(d, 2H, J=8.3Hz), 7.61(d, 2H, J=8.3Hz). 7.78(t, 1H, J=6.3Hz).	DMSO-d6, 300MHz
2-141		221 - 223	0.97- 1.15 (m, 2 H), 1.24 (s, 6 H), 1.25- 1.53 (m, 5 H), 1.58 (s, 6 H), 1.78- 1.93 (m, 4 H), 2.25 (s, 3 H), 2.45- 2.62 (m, 1 H), 3.12 (t, J = 6.4 Hz, 2 H), 5.28 (s, 1 H), 6.83 (br s, 2 H), 7.28 (d, J = 8.3 Hz, 2 H), 7.53- 7.61 (m, 1 H), 7.81 (d, J = 8.3 Hz, 2 H).	DMSO-d6, 300 MHz
2-142		142 - 144	0.99-1.19(m, 2H), 1.34-1.58(m, 3H), 1.60(s, 6H), 1.87-1.99(m, 6H), 2.09(d, 2H, d=6.9 Hz), 2.24(s, 3H), 2.51(m, 1H), 3.63(d, 2H, J=6.6 Hz), 6.81(bra, 2H), 6.99(bra, 1H), 7.24(bra, 1H), 7.30(d, 2H, J=8.3 Hz), 7.62(d, 2H, J=8.3 Hz), 7.96(t, 1H, J=6.6 Hz).	DMSO-d6, 300MHz
2-143		186 - 188	a mixture of 2 conformers: 1.03-1.22(m, 2H), 1.34-1.58(m, 3H), 1.59(s, 6H), 1.72-1.93(m, 6H), 2.13 and 2.27(d, 2H, d=6.9 Hz), 2.24(s, 3H), 2.51(m, 1H), 2.61 and 3.03(s, 3H), 3.88 and 4.09(s, 2H), 6.82(bra, 2H), 7.25(d, 2H, J=8.3 Hz), 7.62(d, 2H, J=8.3 Hz) 11.70(bra, 1H).	DMSO-d6, 300MHz

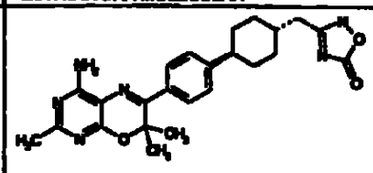
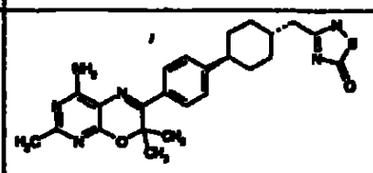
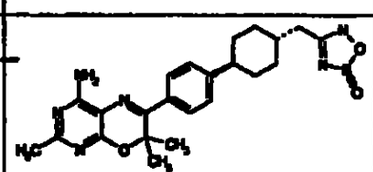
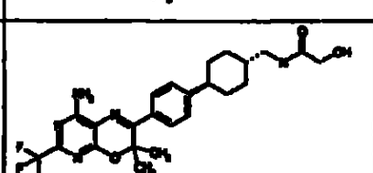
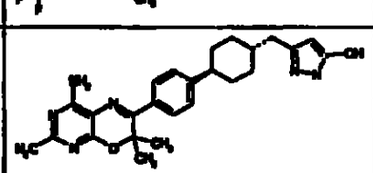
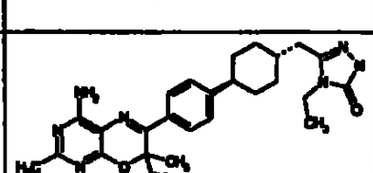
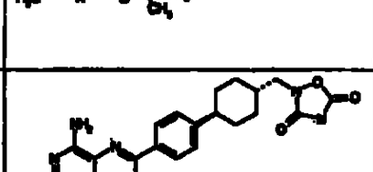
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-144		>250	a rotamer of 2 conformers: 0.98-1.20(m, 2H), 1.34-1.55(m, 2H), 1.69(s, 6H), 1.73-1.83(m, 6H), 2.12 and 2.28(d, 2H, d=6.9 Hz), 2.34(s, 3H), 2.61(m, 1H), 2.79 and 3.09(s, 3H), 3.05 and 3.82(s, 2H), 6.88(bm, 2H), 6.96 and 7.14(bm, 1H), 7.20(d, 2H, J=8.3 Hz), 7.27 and 7.42(bm, 1H), 7.61(d, 2H, J=8.3 Hz).	DMSO-d6, 400MHz
2-145		>250	0.85(s, 3H), 1.21(s, 3H), 1.58(s, 6H), 1.96-2.02(m, 1H), 2.14-2.36(m, 4H), 2.34(s, 3H), 3.14-3.30(m, 1H), 6.83(bm, 2H), 7.18(d, 2H, J=8.0Hz), 7.62(d, 2H, J=8.0Hz)	DMSO-d6, 400MHz
2-146		>250	1.58(s, 6H), 1.74-1.83(m, 2H), 2.24(s, 3H), 2.37(d, 2H, J=8.0Hz), 2.44-2.60(m, 4H), 3.26-3.43(m, 1H), 6.83(bm, 2H), 7.27(d, 2H, J=8.0Hz), 7.61(d, 2H, J=8.0Hz), 11.99(bm, 1H)	DMSO-d6, 400MHz
2-147		>230	1.05-1.30(m, 2H), 1.38-1.53(m, 2H), 1.58(s, 6H), 1.73-1.87(m, 6H), 2.24(s, 3H), 2.29(d, 2H, d=6.8 Hz), 2.91(m, 1H), 6.81(bm, 2H), 7.28(d, 2H, J=8.3 Hz), 7.61(d, 2H, J=8.3 Hz), 11.07(s, 1H), 11.10(bm, 1H).	DMSO-d6, 400MHz
2-148		>250	1.15-1.34(m, 2H), 1.43-1.55(m, 2H), 1.58(s, 6H), 1.83-1.95(m, 4H), 2.24(s, 3H), 2.35-2.41(m, 2H), 2.59-2.66(m, 1H), 6.83(br, 1H), 7.30(d, 2H, J=8.0Hz), 7.62(d, 2H, J=8.0Hz), 11.99(bm, 1H), 15.66(br, 1H)	DMSO-d6, 400MHz
2-149		227 - 230	1.58(s, 6H), 1.60-1.71(m, 4H), 2.04-2.23(m, 2H), 2.23(s, 3H), 2.34(s, 3H), 2.40-2.46(m, 2H), 3.36-3.41(m, 1H), 6.91(bm, 2H), 7.28(d, 2H, J=8.0Hz), 7.61(d, 2H, J=8.0Hz), 11.99(bm, 1H)	DMSO-d6, 400MHz
2-150		228 - 229	0.98-1.10(m, 2H), 1.25(s, 6H), 1.37-1.48(m, 2H), 1.58(s, 6H), 1.76-1.85(m, 6H), 2.34(s, 3H), 2.83-2.87(m, 1H), 2.99-3.06(m, 2H), 5.33(s, 1H), 6.81(bm, 2H), 7.28(d, 2H, J=8.0Hz), 7.58(bm, 1H), 7.62(d, 2H, J=8.0Hz)	DMSO-d6, 400MHz

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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-181		>250	1.11-1.23(m, 2H), 1.43-1.58(m, 2H), 1.57(s, 6H), 1.77-1.88(m, 6H), 2.25(s, 3H), 2.44(d, 2H, J=6.0Hz), 2.53-2.62(m, 1H), 6.81(bra, 2H), 7.28(d, 2H, J=8.0Hz), 7.61(d, 2H, J=8.0Hz), 12.70(bra, 1H)	DMSO-d6, 400MHz
2-182		225 - 228	1.11-1.23(m, 2H), 1.41-1.49(m, 2H), 1.57(s, 6H), 1.78-1.84(m, 6H), 2.24(s, 3H), 2.44(d, 2H, J=6.0Hz), 2.53-2.61(m, 1H), 6.68(bra, 2H), 7.28(d, 2H, J=8.0Hz), 7.61(d, 2H, J=8.0Hz), 12.69(bra, 1H)	DMSO-d6, 400MHz
2-183			1.11-1.24(m, 2H), 1.45-1.51(m, 2H), 1.58(s, 6H), 1.77-1.87(m, 6H), 2.24(s, 3H), 2.46(d, 2H, J=6.0Hz), 2.53-2.58(m, 1H), 6.81(bra, 2H), 7.28(d, 2H, J=8.0Hz), 7.61(d, 2H, J=8.0Hz), 11.41(bra, 1H)	DMSO-d6, 400MHz
2-184		229 - 233	1.09-1.11(m, 2H), 1.37-1.55(m, 3H), 1.58(s, 6H), 1.78-1.87(m, 4H), 2.49-2.57(m, 1H), 2.99-3.04(m, 2H), 3.81(d, 2H, J=6.0Hz), 5.49(t, 1H, J=6.0Hz), 7.32(d, 2H, J=8.0Hz), 7.69(d, 2H, J=8.0Hz)	DMSO-d6, 300MHz
2-185			1.01-1.22(m, 2H), 1.34-1.52(m, 2H), 1.57(s, 6H), 1.68-1.85(m, 4H), 2.24(s, 3H), 2.37(d, 2H, J=6.9 Hz), 2.50(m, 1H), 6.23(s, 1H), 6.81(bra, 2H), 7.27(d, 2H, J=8.3 Hz), 7.60(d, 2H, J=8.3 Hz), 9.25(bra, 1H), 11.20(bra, 1H).	DMSO-d6, 400MHz
2-186		>250	1.09-1.23(m, 2H), 1.18(t, 3H, J=8.0Hz), 1.43-1.52(m, 2H), 1.57(s, 6H), 1.71-1.93(m, 6H), 2.24(s, 3H), 2.44(d, 2H, J=8.0Hz), 2.53-2.58(m, 1H), 3.58(q, 2H, J=8.0Hz), 6.80(bra, 2H), 7.28(d, 2H, J=8.0Hz), 7.60(d, 2H, J=8.0Hz), 11.34(s, 1H)	DMSO-d6, 400MHz
2-187			1.11-1.24(m, 2H), 1.44-1.54(m, 2H), 1.58(s, 6H), 1.68-1.87(m, 6H), 2.24(s, 3H), 2.53-2.57(m, 1H), 3.51(d, 2H, J=8.0Hz), 6.80(bra, 2H), 7.28(d, 2H, J=8.0Hz), 7.61(d, 2H, J=8.0Hz), 12.28(bra, 1H)	DMSO-d6, 400MHz

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Tabla 2 (Continuación)

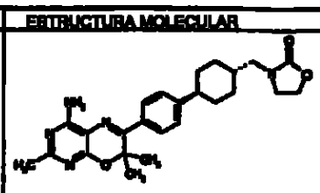
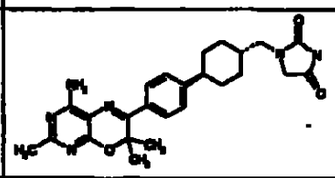
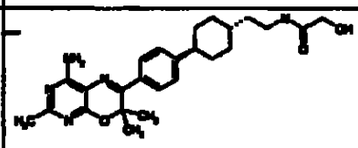
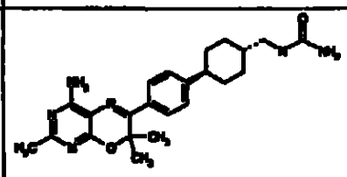
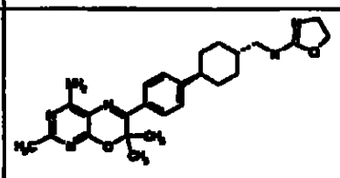
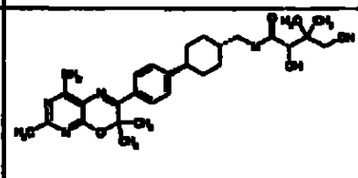
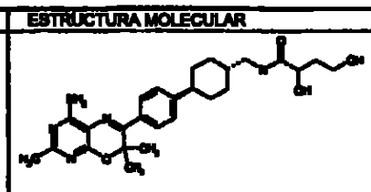
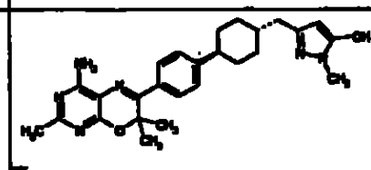
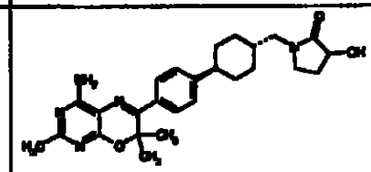
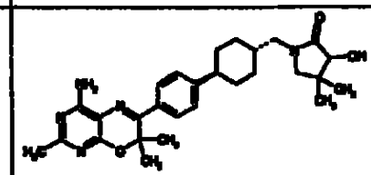
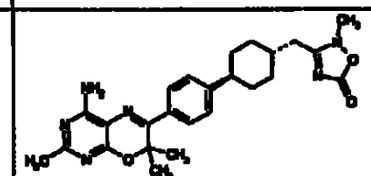
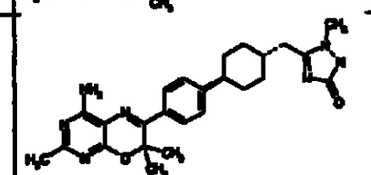
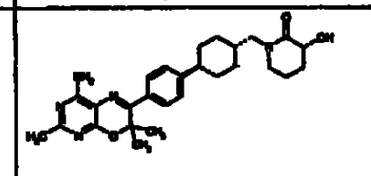
NUEVO EJEMPLO #	EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-	158		240-241	1.03-1.14(m, 2H), 1.41-1.53(m, 2H), 1.58-1.71(m, 1H), 1.65(s, 6H), 1.77-1.88(m, 4H), 2.25(s, 3H), 2.50-2.58(m, 1H), 3.04(d, 2H, J=8.0Hz), 3.98(t, 2H, J=7.5Hz), 4.27(t, 2H, J=7.5Hz), 6.58(br, 1H), 7.28(d, 2H, J=8.0Hz), 7.53(d, 2H, J=8.0Hz)	DMSO-d6, 300MHz
2-	159		148(desc.)	1.01-1.13(m, 2H), 1.36-1.51(m, 2H), 1.58-1.68(m, 1H), 1.65(s, 6H), 1.76-1.88(m, 4H), 2.25(s, 3H), 2.50-2.57(m, 1H), 3.11(d, 2H, J=8.0Hz), 3.98(s, 2H), 6.61(br, 1H), 7.28(d, 2H, J=8.0Hz), 7.53(d, 2H, J=8.0Hz)	DMSO-d6, 300MHz
2-	160		185-186	1.00-1.13(m, 2H), 1.30-1.51(m, 6H), 1.65(s, 6H), 1.76-1.87(m, 4H), 2.24(s, 3H), 2.50-2.58(m, 1H), 3.00-3.09(m, 2H), 3.17(s, 2H, J=7.5Hz), 3.78(d, 2H, J=8.0Hz), 5.40(t, 1H, J=8.0Hz), 6.59(br, 2H), 7.29(d, 2H, J=8.0Hz), 7.52(d, 2H, J=8.0Hz), 7.56(t, 1H, J=8.0Hz)	DMSO-d6, 300MHz
2-	161		219 - 221	0.99-1.13(m, 2H), 1.36-1.52(m, 2H), 1.65(s, 6H), 1.73-1.91(m, 4H), 2.24(s, 3H), 2.47-2.57(m, 1H), 2.89(t, 2H, J=6.2Hz), 6.33(br, 2H), 6.96(t, 1H, J=5.7Hz), 6.99(br, 2H), 7.29(d, 2H, J=8.3Hz), 7.51(d, 2H, J=8.3Hz)	DMSO-d6, 300MHz
2-	162		218 - 220	0.99-1.11(m, 2H), 1.36-1.53(m, 2H), 1.65(s, 6H), 1.76-1.90(m, 4H), 2.24(s, 3H), 2.46-2.59(m, 1H), 2.81(d, 2H, J=6.6Hz), 3.99(t, 2H, J=6.6Hz), 4.13(t, 2H, J=6.6Hz), 6.76(br, 2H), 7.29(d, 2H, J=8.3Hz), 7.51(d, 2H, J=8.3Hz)	DMSO-d6, 300MHz
2-	163		219 - 221	0.83(s, 3H), 0.93(s, 3H), 0.99-1.14(m, 2H), 1.36-1.54(m, 2H), 1.65(s, 6H), 1.76-1.89(m, 4H), 2.24(s, 3H), 2.44-2.59(m, 1H), 2.94-3.10(m, 2H), 3.16-3.34(m, 2H), 3.73(d, 1H, J=8.7Hz), 4.49(t, 1H, J=8.7Hz), 6.31(d, 1H, J=8.7Hz), 6.76(br, 2H), 7.29(d, 2H, J=8.3Hz), 7.51(d, 2H, J=8.3Hz), 7.58(t, 1H, J=8.6Hz)	DMSO-d6, 300MHz

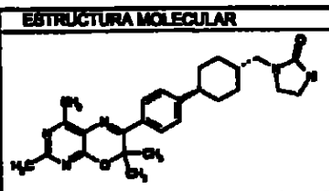
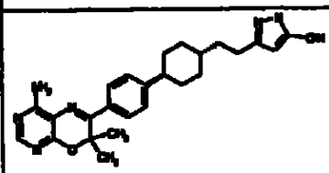
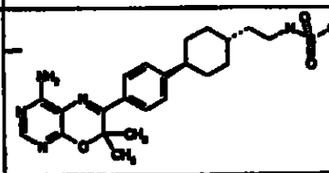
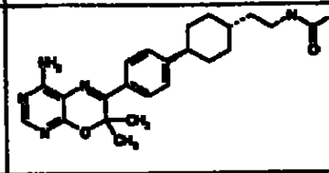
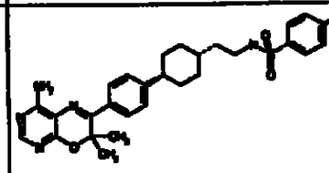
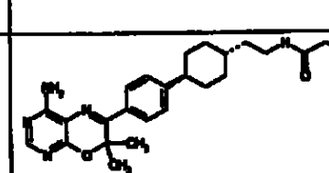
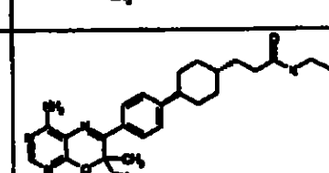
Tabla 2 (Continuación)

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NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-164		222 - 225	0.99-1.14(m, 2H), 1.35-1.51(m, 4H), 1.58(s, 6H), 1.75-1.85(m, 6H), 2.24(s, 3H), 2.45-2.59(m, 1H), 2.98(t, 2H, J=6.6Hz), 3.45-3.54(m, 2H), 3.98(dd, 1H, J=6.7, 3.8Hz), 4.42(t, 1H, J=6.7Hz), 5.35(d, 1H, J=6.7Hz), 6.81(br, 2H), 7.29(d, 2H, J=8.3Hz), 7.61(d, 2H, J=8.3Hz), 7.69(t, 1H, J=6.3Hz)	DMSO-d6, 300MHz
2-165		>250	a mixture of 2 conformers;1.02-1.16(m, 2H), 1.37-1.48(m, 2H), 1.57(s, 6H), 1.75-1.85(m, 5H), 2.24(s, 3H), 2.27(d, 2H, J=4.0Hz), 2.53-2.58(m, 1H), 3.30 and 3.55(s, 3H), 5.12(m, 1H), 6.81(bs, 2H), 7.27(d, 2H, J=8.0Hz), 7.60(d, 2H, J=8.5Hz), 10.84(bs, 1H)	DMSO-d6, 400MHz
2-166		226 - 233	0.99-1.13(m, 2H), 1.35-1.51(m, 2H), 1.58(s, 6H), 1.83-1.87(m, 6H), 2.21-2.32(m, 1H), 2.24(s, 3H), 2.45-2.60(m, 1H), 3.55(d, 2H, J=7.1Hz), 3.17-3.35(m, 2H), 4.04-4.18(m, 1H), 5.45(br, 1H), 6.82(br, 2H), 7.29(d, 2H, J=8.3Hz), 7.62(d, 2H, J=8.3Hz)	DMSO-d6, 300MHz
2-167			0.90(s, 3H), 0.99-1.14(m, 2H), 1.09(s, 3H), 1.30-1.51(m, 2H), 1.58(s, 6H), 1.82-1.90(m, 6H), 2.24(s, 3H), 2.45-2.59(m, 1H), 2.95-3.13(m, 4H), 3.74(d, 1H, J=8.7Hz), 5.41(d, 1H, J=5.7Hz), 6.79(br, 2H), 7.29(d, 2H, J=8.3Hz), 7.61(d, 2H, J=8.3Hz)	DMSO-d6, 300MHz
2-168			1.13-1.31(m, 2H), 1.35-1.58(m, 2H), 1.58(s, 6H), 1.74-1.82(m, 5H), 2.25(s, 3H), 2.53(m, 1H), 2.58(d, 2H, d=6.9 Hz), 3.72(s, 3H), 6.80(bm, 2H), 7.28(d, 2H, J=8.3 Hz), 7.62(d, 2H, J=8.3 Hz).	DMSO-d6, 300MHz
2-169		>230	1.10-1.25(m, 2H), 1.35-1.53(m, 2H), 1.57(s, 6H), 1.69-1.87(m, 6H), 2.24(s, 3H), 2.50(m, 1H), 2.54(d, 2H, d=6.9 Hz), 3.68(s, 3H), 6.80(bm, 2H), 7.27(d, 2H, J=8.3 Hz), 7.60(d, 2H, J=8.3 Hz), 10.66(bm, 1H).	DMSO-d6, 400MHz
2-170		228 - 229	1.05-1.15(m, 2H), 1.38-1.48(m, 2H), 1.58(s, 6H), 1.66-2.01(m, 7H), 2.24(s, 3H), 2.51-2.55(m, 1H), 3.08-3.30(m, 6H), 3.85-3.90(m, 2H), 4.97(d, 1H, J=4.0Hz), 6.80(bm, 2H), 7.27(d, 2H, J=8.0Hz), 7.61(d, 2H, J=12.0Hz)	DMSO-d6, 400MHz

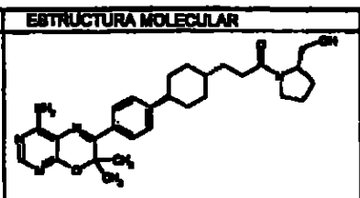
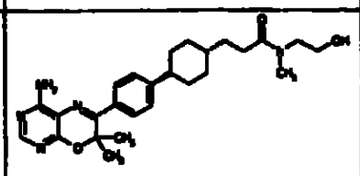
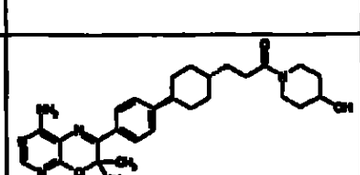
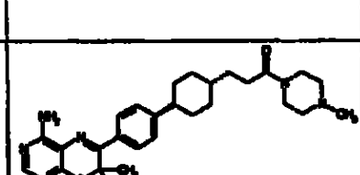
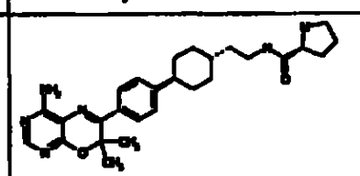
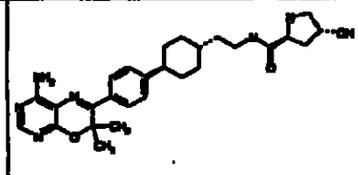
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-171			1.09-1.29(m, 2H), 1.38-1.60(m, 2H), 1.69(s, 6H), 1.84-2.04(m, 4H), 2.44(s, 2H), 2.48-2.60(m, 1H), 3.05(d, 2H, J=6.0Hz), 3.36-3.83(m, 4H), 4.56(s, 1H), 6.80(br, 2H), 7.24(d, 2H, J=8.3Hz), 7.54(d, 2H, J=8.3Hz)	CDCl3, 300MHz
2-172		>250	1.04-1.09(m, 2H), 1.43(m, 1H), 1.43-1.80(m, 4H), 1.60(s, 6H), 1.80-1.93(m, 4H), 5.24(s, 1H), 6.68(brs, 2H), 7.20(d, 2H, J=8.3 Hz), 7.62(d, 2H, J=8.3 Hz), 7.84(s, 1H), 9.20(brs, 1H), 11.20(brs, 1H).	DMSO-d6, 400MHz
2-173		218 - 219	1.03-1.13(m, 2H), 1.46-1.48(m, 6H), 1.60(s, 6H), 1.81-1.85(m, 4H), 2.53-2.57(m, 1H), 2.80(s, 3H), 2.89-3.03(m, 2H), 6.65-6.97(m, 3H), 7.31(d, 2H, J=8.0Hz), 7.69(d, 2H, J=8.0Hz), 7.88(s, 1H)	DMSO-d6, 300
2-174		238 - 239	0.98-1.14(m, 2H), 1.31-1.52(m, 6H), 1.60(s, 6H), 1.78(s, 3H), 1.80-1.85(m, 4H), 2.53-2.59(m, 1H), 3.05-3.12(m, 2H), 6.93(brs, 2H), 7.30(d, 2H, J=8.0Hz), 7.68(d, 2H, J=8.0Hz), 7.77(t, 1H, J=4.5Hz), 7.85(s, 1H)	DMSO-d6, 300
2-175		230 - 231	0.91-1.06(m, 2H), 1.27-1.45(m, 6H), 1.60(s, 6H), 1.67-1.82(m, 4H), 2.39(s, 3H), 2.44-2.48(m, 1H), 2.74-2.80(m, 2H), 6.93(brs, 2H), 7.29(d, 2H, J=8.0Hz), 7.41(d, 2H, J=8.0Hz), 7.45(t, 1H, J=7.5Hz), 7.64(d, 2H, J=8.0Hz), 7.68(d, 2H, J=8.0Hz), 7.86(s, 1H)	DMSO-d6, 300
2-176		195 - 196	0.98-1.14(m, 2H), 1.29-1.55(m, 11H), 1.78-1.83(m, 4H), 2.51-2.58(m, 1H), 3.14-3.21(m, 2H), 3.76(d, 2H, J=6.0Hz), 6.36(t, 1H, J=6.0Hz), 6.92(brs, 2H), 7.30(d, 2H, J=8.0Hz), 7.62-7.67(m, 2H), 7.90(s, 1H)	DMSO-d6, 300
2-177		199 - 200	0.84(t, 3H, J=7.4Hz), 0.97-1.12(m, 2H), 1.18-1.53(m, 7H), 1.60(s, 6H), 1.78-1.88(m, 4H), 2.10(t, 2H, J=7.7Hz), 2.48-2.57(m, 1H), 2.89(s, 2H, J=6.0Hz), 6.94(br, 2H), 7.28(d, 2H, J=8.3Hz), 7.64(d, 2H, J=8.3Hz), 7.75(t, 1H, J=6.8Hz), 7.93(s, 1H)	DMSO-d6, 300MHz

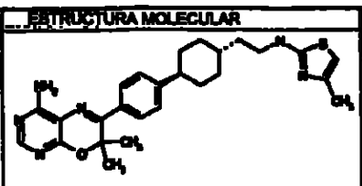
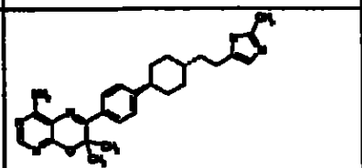
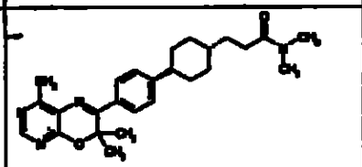
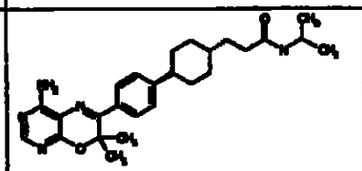
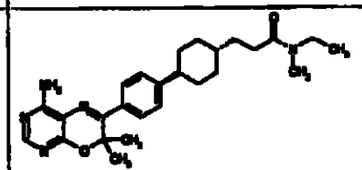
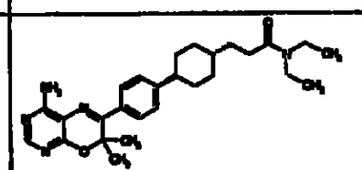
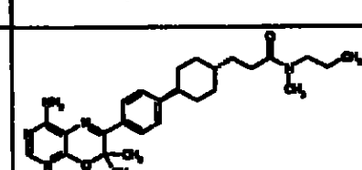
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-176		143 - 160	1.03-1.17(m, 2H), 1.35-1.59(m, 6H), 1.64(s, 6H), 2.30(t, 1.2H, J=7.7Hz), 2.39(t, 0.8H, J=7.7Hz), 2.51-2.63(m, 1H), 3.17-3.54(m, 6H), 3.89-4.03(m, 1H), 4.77(br, 0.6H), 4.86(br, 0.4H), 6.99(br, 2H), 7.23(d, 2H, J=8.3Hz), 7.67(d, 2H, J=8.3Hz), 7.99(s, 1H)	DMSO-d6, 300MHz
2-179		165 - 170	0.98-1.16(m, 2H), 1.35-1.58(m, 6H), 1.60(s, 6H), 1.75-1.94(m, 4H), 2.24-2.44(m, 2H), 2.48-2.60(m, 1H), 2.51(s, 1.5H), 3.00(s, 1.5H), 3.25-3.41(m, 2H), 3.43-3.55(m, 2H), 4.60(br, 0.5H), 4.79(br, 0.5H), 6.93(br, 2H), 7.30(d, 2H, J=8.4Hz), 7.64(d, 2H, J=8.4Hz), 7.99(s, 1H)	DMSO-d6, 300MHz
2-180		200 - 202	0.98-1.55(m, 8H), 1.60(s, 6H), 1.81-1.94(m, 6H), 2.33(t, 2H, J=7.6Hz), 2.48-2.60(m, 1H), 2.93-3.04(m, 1H), 3.07-3.30(m, 1H), 3.60-3.75(m, 2H), 3.85-4.03(m, 1H), 4.71(br, 1H), 6.93(br, 2H), 7.30(d, 2H, J=8.4Hz), 7.64(d, 2H, J=8.4Hz), 7.99(s, 1H)	DMSO-d6, 300MHz
2-181		83 - 207	1.03-1.14(m, 2H), 1.24-1.51(m, 6H), 1.60(s, 6H), 1.77-1.91(m, 4H), 2.16-2.37(m, 6H), 2.48-2.54(m, 1H), 3.33-3.50(m, 4H), 6.93(br, 2H), 7.29(d, 2H, J=8.3Hz), 7.64(d, 2H, J=8.3Hz), 7.99(s, 1H)	DMSO-d6, 300MHz
2-182		167 - 169	0.98-1.13(m, 2H), 1.27-1.50(m, 6H), 1.55-1.69(m, 6H), 1.76-2.00(m, 5H), 2.51-2.57(m, 1H), 2.80-2.87(m, 2H), 3.09-3.16(m, 2H), 3.49-3.63(m, 1H), 6.94(brs, 2H), 7.29(d, 2H, J=8.0Hz), 7.63(d, 2H, J=8.0Hz), 7.68-7.82(m, 1H), 7.99(s, 1H)	DMSO-d6, 300
2-183		201 - 203	0.98-1.13(m, 2H), 1.24-1.70(m, 12H), 1.77-1.99(m, 6H), 2.51-2.59(m, 1H), 2.71-2.87(m, 2H), 3.07-3.16(m, 2H), 3.70(t, 1H, J=7.5Hz), 4.17(brs, 1H), 4.67(d, 1H, J=3.0Hz), 6.93(brs, 2H), 7.30(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.82(t, 1H, J=4.5Hz), 7.99(s, 1H)	DMSO-d6, 300

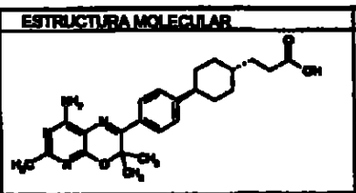
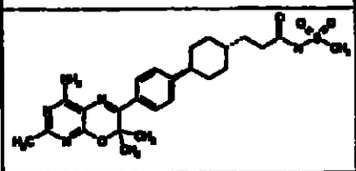
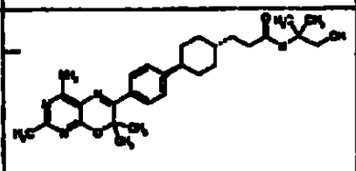
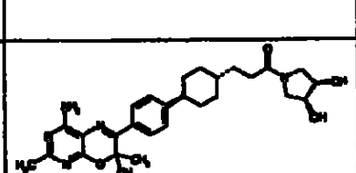
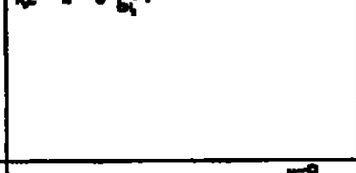
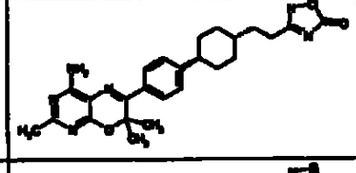
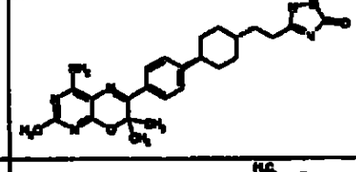
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-184		>250	1.03-1.17(m, 2H), 1.37-1.54(m, 6H), 1.60(s, 6H), 1.75-1.90(m, 4H), 2.09(s, 3H), 2.53-2.60(m, 1H), 3.19-3.25(m, 2H), 6.12(brs, 1H), 6.94(brs, 2H), 7.30(d, 2H, J=8.0Hz), 7.34-7.39(m, 1H), 7.84(d, 2H, J=8.0Hz), 7.85(s, 1H)	DMSO-d6, 300
2-185		193 - 194	1.02-1.14(m, 2H), 1.27-1.51(m, 6H), 1.60(s, 6H), 1.69-1.80(m, 4H), 2.20(s, 3H), 2.44-2.48(m, 2H), 2.52-2.56(m, 1H), 6.83(s, 1H), 6.96(brs, 2H), 7.29(d, 2H, J=12.0Hz), 7.62(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-186		200 - 201	0.98-1.13(m, 2H), 1.35-1.51(m, 6H), 1.60(s, 6H), 1.77-1.90(m, 4H), 2.31(s, 3H, J=7.7Hz), 2.50-2.57(m, 1H), 2.81(s, 3H), 2.97(s, 3H), 6.93(br, 2H), 7.30(d, 2H, J=8.1Hz), 7.64(d, 2H, J=8.1Hz), 7.88(s, 1H)	DMSO-d6, 300MHz
2-187		208 - 209	0.98-1.11(m, 2H), 1.04(d, 6H, J=6.6Hz), 1.20-1.51(m, 6H), 1.60(s, 6H), 1.75-1.92(m, 4H), 2.07(t, 2H, J=7.2Hz), 2.48-2.58(m, 1H), 3.83(sd, 1H, J=20.8, 6.6Hz), 6.93(br, 2H), 7.30(d, 2H, J=8.0Hz), 7.62(s, 1H, J=7.2Hz), 7.84(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 300MHz
2-188		173 - 175	0.98(t, 1.5H, J=7.1Hz), 1.01-1.15(m, 2H), 1.10(t, 1.5H, J=7.1Hz), 1.22-1.54(m, 6H), 1.60(s, 6H), 1.75-1.87(m, 4H), 2.38(q, 1H, J=7.1Hz), 2.32(t, 1H, J=7.1Hz), 2.48-2.58(m, 1H), 2.78(q, 1.5H), 2.94(q, 1.5H), 3.29-3.37(m, 2H), 6.93(br, 2H), 7.30(d, 2H, J=8.4Hz), 7.84(d, 2H, J=8.4Hz), 7.88(s, 1H)	DMSO-d6, 300MHz
2-189		192 - 194	0.98-1.13(m, 2H), 1.00(t, 3H, J=7.0Hz), 1.11(t, 3H, J=7.0Hz), 1.35-1.53(m, 6H), 1.60(s, 6H), 1.75-1.92(m, 4H), 2.30(t, 2H, J=7.7Hz), 2.48-2.58(m, 1H), 3.22-3.34(m, 4H), 6.94(br, 2H), 7.30(d, 2H, J=8.4Hz), 7.84(d, 2H, J=8.4Hz), 7.88(s, 1H)	DMSO-d6, 300MHz
2-190		210- 212	0.80(t, 1.5H, J=7.3Hz), 0.84(t, 1.5H, J=7.3Hz), 0.98-1.15(m, 2H), 1.22-1.57(m, 6H), 1.60(s, 6H), 1.74-1.91(m, 4H), 2.28-2.37(m, 2H), 2.47-2.58(m, 1H), 2.76(s, 1.5H), 2.95(s, 1.5H), 3.24(q, 2H, J=7.3Hz), 6.93(br, 2H), 7.30(d, 2H, J=8.4Hz), 7.84(d, 2H, J=8.4Hz), 7.93(s, 1H)	DMSO-d6, 300MHz

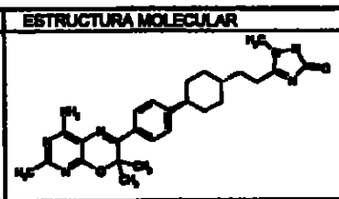
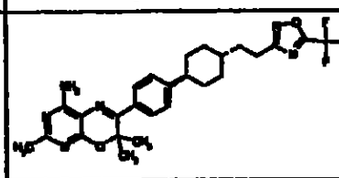
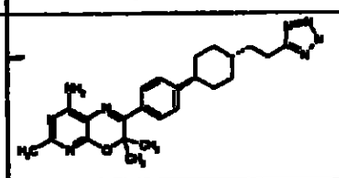
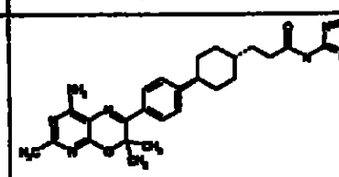
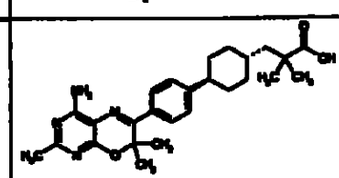
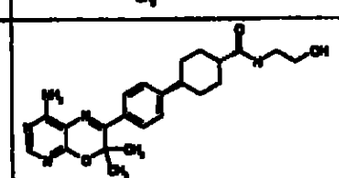
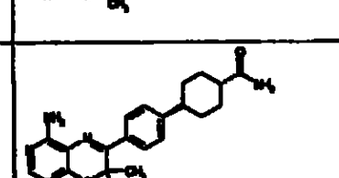
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F	NMR(A)	SOLVENTE
2-191		>250	1.00-1.11(m, 2H), 1.25-1.36(m, 1H), 1.43-1.80(m, 4H), 1.58(s, 6H), 1.76-1.88(m, 4H), 2.22-2.38(m, 2H), 2.34(s, 3H), 6.82(brs, 2H), 7.28(d, 2H, J=8.0Hz), 7.62(d, 2H, J=8.0Hz), 11.98(brs, 1H)	DMSO-d6, 300MHz
2-192		>250	0.98-1.12(m, 2H), 1.22-1.33(m, 1H), 1.42-1.83(m, 4H), 1.58(s, 6H), 1.88-1.94(m, 4H), 2.34(s, 3H), 2.33(t, 2H, J=7.5Hz), 3.23(s, 3H), 6.81(brs, 2H), 7.28(d, 2H, J=8.0Hz), 7.62(d, 2H, J=8.0Hz), 11.98(brs, 1H)	DMSO-d6, 300MHz
2-193		>240	0.98-1.12(m, 2H), 1.17(s, 6H), 1.21-1.30(m, 1H), 1.35-1.48(m, 4H), 1.58(s, 6H), 1.77-1.87(m, 4H), 2.03(t, 2H, J=7.5Hz), 2.34(s, 3H), 2.47-2.59(m, 1H), 3.37(d, 2H, J=6.0Hz), 4.58(t, 1H, J=6.0Hz), 6.82(br, 2H), 7.24(brs, 1H), 7.28(d, 2H, J=8.0Hz), 7.62(d, 2H, J=8.0Hz)	DMSO-d6, 300MHz
2-194		230 - 231	0.98-1.12(m, 2H), 1.25-1.36(m, 1H), 1.37-1.52(m, 4H), 1.58(s, 6H), 1.78-1.87(m, 4H), 2.22(t, 2H, J=7.5Hz), 2.34(s, 3H), 2.49-2.57(m, 1H), 3.17(dd, 1H, J=12.0, 6.0Hz), 3.25(dd, 1H, J=12.0, 6.0Hz), 3.35(dd, 1H, J=12.0, 6.0Hz), 3.57(dd, 1H, J=12.0, 6.0Hz), 3.94-4.01(m, 1H), 4.01-4.08(m, 1H), 4.58(d, 1H, J=6.0Hz), 4.93(d, 1H, J=6.0Hz), 6.81(br, 1H), 7.28(d, 2H, J=8.0Hz), 7.62(d, 2H, J=8.0Hz)	DMSO-d6, 300MHz
2-195		250(dec.)	1.05-1.13(m, 2H), 1.43-1.84(m, 6H), 1.58(s, 6H), 1.84(m, 4H), 2.24(s, 3H), 2.55(t, 2H, J=7.5Hz), 6.83(brs, 2H), 7.28(d, 2H, J=8.3Hz), 7.62(d, 2H, J=8.3Hz).	DMSO-d6, 400MHz
2-196		211(dec.)	1.05-1.13(m, 2H), 1.44-1.84(m, 6H), 1.58(s, 6H), 1.84(m, 4H), 2.24(s, 3H), 2.55(t, 2H, J=7.5Hz), 6.83(brs, 2H), 7.28(d, 2H, J=8.3Hz), 7.62(d, 2H, J=8.3Hz).	DMSO-d6, 300MHz
2-197		250(dec.)	1.04-1.16(m, 2H), 1.38-1.48(m, 6H), 1.58(s, 6H), 1.88(m, 4H), 2.24(m, 2H), 2.84(m, 1H), 2.88(m, 2H), 3.69(s, 3H), 6.83(brs, 2H), 7.28(d, 2H, J=8.3Hz), 7.62(d, 2H, J=8.3Hz).	DMSO-d6, 300MHz

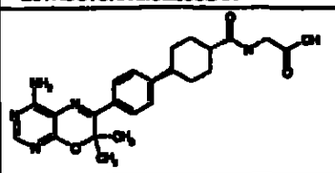
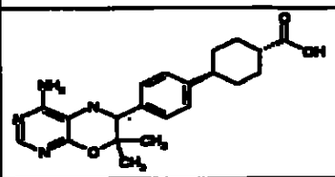
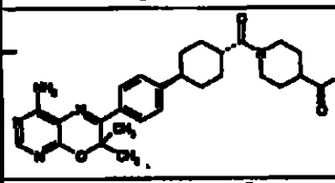
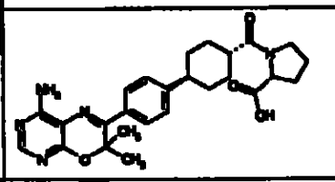
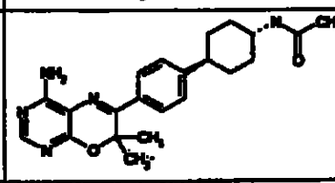
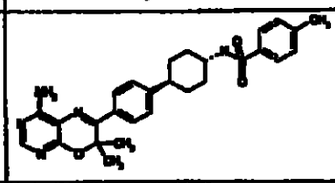
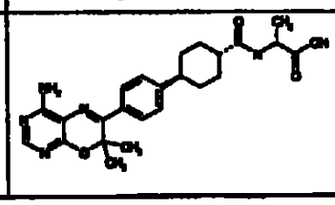
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-198		>280	1.04-1.11(m, 2H), 1.28-1.52(m, 6H), 1.58(s, 6H), 1.88(m, 4H), 2.54(s, 3H), 2.64(m, 2H), 3.57(s, 3H), 4.68(t, 1H, J=5.3Hz), 6.83(m, 2H), 7.20(d, 2H, J=8.3Hz), 7.44(s, 1H, J=5.6Hz), 7.62(d, 2H, J=8.3Hz).	DMSO-d6, 300MHz
2-199		198 - 200	1.10-1.15(m, 2H), 1.43-1.60(m, 3H), 1.69(s, 6H), 1.76(m, 2H), 1.94(m, 4H), 2.47(s, 3H), 2.67(m, 1H), 2.90(m, 2H), 6.74(m, 2H), 7.22(d, 2H, J=8.3Hz), 7.64(d, 2H, J=8.3Hz).	CDCl3, 300MHz
2-200		>280	1.04-1.18(m, 2H), 1.37-1.58(m, 2H), 1.58(s, 6H), 1.62-1.89(m, 2H), 1.79-1.91(m, 4H), 2.24(s, 3H), 2.47-2.58(m, 1H), 2.83(d, 2H, J=7.6Hz), 6.81(ms, 2H), 7.20(d, 2H, J=8.0Hz), 7.62(d, 2H, J=8.0Hz)	DMSO-d6, 300MHz
2-201		>280	1.03-1.18(m, 2H), 1.27-1.41(m, 1H), 1.39-1.53(m, 4H), 1.58(s, 6H), 1.81-1.87(m, 4H), 2.24(s, 3H), 2.48-2.53(m, 2H), 2.57(br, 1H), 6.81(br, 1H), 7.20(d, 2H, J=8.0Hz), 7.62(d, 2H, J=8.0Hz), 11.98(ms, 1H), 15.78(br, 1H)	DMSO-d6, 300MHz
2-202		>225	1.02-1.18(m, 2H), 1.11(s, 6H), 1.34-1.53(m, 6H), 1.58(s, 6H), 1.69-1.85(m, 4H), 2.24(s, 3H), 2.43-2.53(m, 1H), 6.81(br, 2H), 7.20(d, 2H, J=8.3Hz), 7.61(d, 2H, J=8.3Hz), 12.03(brs, 1H)	DMSO-d6, 300MHz
2-203		235 - 237	1.35-1.55(m, 4H), 1.58(s, 6H), 1.77-1.78(m, 4H), 2.15-2.29(m, 1H), 2.48-2.61(m, 1H), 3.11(q, 2H, J=6.0Hz), 3.39(q, 2H, J=6.0Hz), 4.64(t, 1H, J=6.0Hz), 6.87(br, 2H), 7.21(d, 2H, J=8.4Hz), 7.58(d, 2H, J=8.4Hz), 7.74(t, 1H, J=6.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-204		>280	1.43-1.54(m, 4H), 1.58(s, 6H), 1.81-1.95(m, 4H), 2.10-2.34(m, 1H), 2.48-2.62(m, 1H), 6.70(brs, 1H), 6.85(br, 2H), 7.23(brs, 1H), 7.31(d, 2H, J=8.4Hz), 7.65(d, 2H, J=8.4Hz), 7.90(s, 1H)	DMSO-d6, 300MHz

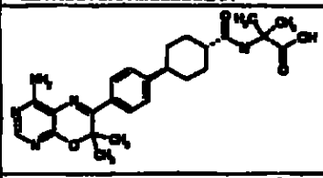
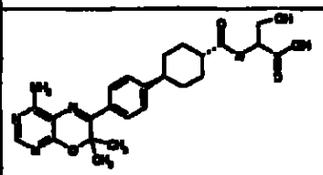
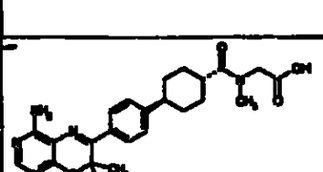
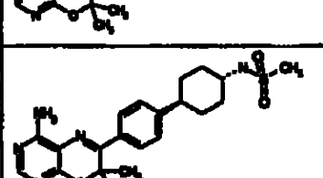
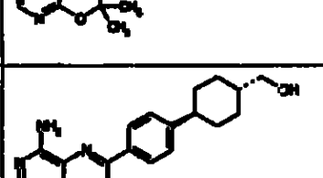
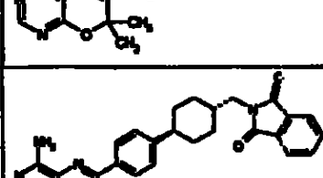
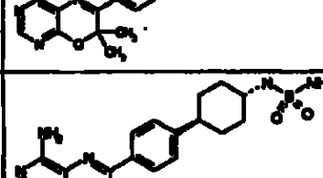
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-206		>250	1.41-1.55(m, 4H), 1.51(s, 6H), 1.81-1.91(m, 4H), 2.21-2.31(m, 1H), 2.84-2.90(m, 1H), 3.74(d, 2H, J=5.5Hz), 6.97(br, 2H), 7.31(d, 2H, J=8.1Hz), 7.66(d, 2H, J=8.1Hz), 7.98(s, 1H), 8.04(t, 1H, J=5.5Hz)	DMSO-d6, 400MHz
2-208		>250	1.09(s, 3H), 1.22(s, 3H), 1.41-1.84(m, 4H), 1.80-1.90(m, 2H), 1.89-2.04(m, 2H), 2.22-2.30(m, 1H), 2.47-2.55(m, 1H), 4.11(s, 1H), 6.27(s, 1H), 6.23(s, 2H), 7.25(d, 2H, J=8.1Hz), 7.36(d, 2H, J=8.1Hz), 7.62(s, 1H)	DMSO-d6, 400MHz
2-207		>250	1.45-1.55(m, 7H), 1.60(s, 6H), 1.80-1.90(m, 6H), 2.60-2.70(m, 2H), 3.05-3.20(m, 1H), 3.85-4.30(m, 2H), 6.90(bs, 2H), 7.30(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.95(s, 1H), 12.05(bs, 1H)	DMSO-d6, 300MHz
2-209		163 - 164	1.45-1.55(m, 4H), 1.50(s, 6H), 1.80-1.95(m, 7H), 2.05-2.15(m, 2H), 2.63-2.83(m, 1H), 3.55-3.63(m, 2H), 4.21-4.29(m, 1H), 6.95(bs, 2H), 7.35(d, 2H, J=8.0Hz), 7.66(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-208		>250	1.23-1.38(m, 2H), 1.45-1.57(m, 2H), 1.60(s, 6H), 1.78(s, 3H), 1.85-1.92(m, 4H), 2.53-2.65(m, 1H), 3.58-3.66(m, 1H), 6.94(bs, 2H), 7.33(d, 2H, J=8.0Hz), 7.66(d, 2H, J=8.0Hz), 7.76(d, 1H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-210		>250	1.24-1.46(m, 4H), 1.55(s, 6H), 1.69-1.78(m, 4H), 2.39(s, 3H), 2.41-2.46(m, 1H), 2.99-3.09(m, 1H), 6.93(bs, 2H), 7.27(d, 2H, J=8.0Hz), 7.40(d, 2H, J=8.0Hz), 7.61(d, 2H, J=8.0Hz), 7.66(d, 1H, J=8.0Hz), 7.73(d, 2H, J=8.0Hz), 7.94(s, 1H)	DMSO-d6, 300
2-211		>250	a mixture of 2 conformers: 1.25 and 1.27(s, 3H), 1.43-1.57(m, 4H), 1.51(s, 6H), 1.78-1.91(m, 4H), 2.21-2.30(m, 1H), 2.52-2.63(m, 1H), 4.14-4.22(m, 1H), 6.99(bs, 2H), 7.32(d, 2H, J=8.0Hz), 7.65(d, 2H, J=8.0Hz), 7.95(s, 1H), 8.04(d, 1H, J=8.0Hz)	DMSO-d6, 300MHz

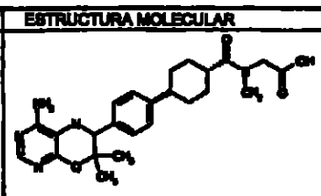
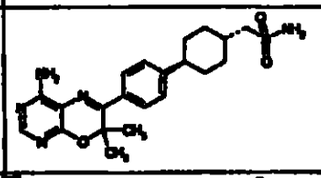
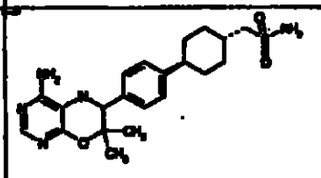
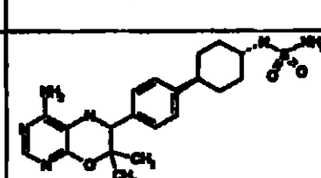
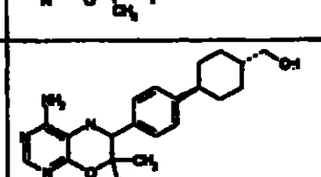
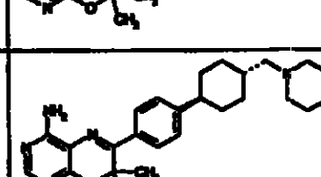
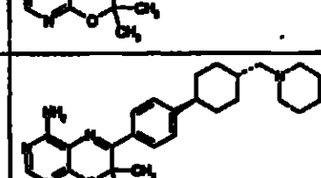
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-212		>250	1.33(s, 6H), 1.42-1.54(m, 4H), 1.60(s, 6H), 1.81-1.89(m, 4H), 2.17-2.25(m, 1H), 2.53-2.59(m, 1H), 6.87(bs, 2H), 7.31(d, 2H, J=8.0Hz), 7.65(d, 2H, J=8.0Hz), 7.80(bs, 1H), 7.85(s, 1H)	DMSO-d6, 300MHz
2-213		>250	1.46-1.57(m, 4H), 1.61(s, 6H), 1.84-1.91(m, 4H), 2.30-2.37(m, 1H), 2.53-2.60(m, 1H), 3.50-3.70(m, 2H), 4.25-4.31(m, 1H), 4.91(bs, 1H), 6.87(bs, 2H), 7.32(d, 2H, J=8.0Hz), 7.65(d, 2H, J=8.0Hz), 7.69(d, 1H, J=8.0Hz), 7.86(s, 1H)	DMSO-d6, 300MHz
2-214		>250	a mixture of 2 conformers: 1.49-1.53(m, 4H), 1.61(s, 6H), 1.80-1.89(m, 4H), 2.51 and 3.09(s, 3H), 3.66 and 4.29(s, 2H), 6.83(bs, 2H), 7.31 and 7.33(d, 2H, J=8.0Hz), 7.69 and 7.85(d, 2H, J=8.0Hz), 7.85(s, 1H)	DMSO-d6, 300MHz
2-215		>250	1.34-1.44(m, 2H), 1.51-1.58(m, 2H), 1.60(s, 6H), 1.76-1.87(m, 2H), 1.97-2.06(m, 2H), 2.51-2.55(m, 1H), 2.93(s, 3H), 3.19-3.23(m, 1H), 6.80(bs, 2H), 7.53(d, 1H, J=8.0Hz), 7.31(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.85(s, 1H)	DMSO-d6, 400
2-216			1.01-1.10(m, 2H), 1.46-1.48(m, 3H), 1.60(s, 6H), 1.83-1.87(m, 4H), 2.52-2.55(m, 1H), 3.22-3.26(m, 2H), 6.80(bs, 2H), 7.30(d, 2H, J=8.0Hz), 7.63(d, 2H, J=8.0Hz), 7.84(s, 1H)	DMSO-d6, 400
2-217		225 - 227	1.05-1.20(m, 2H), 1.35-1.48(m, 2H), 1.58(s, 6H), 1.78-1.81(m, 2H), 2.53-2.59(m, 1H), 3.48(d, 2H, J=6.0Hz), 6.69(bs, 2H), 7.27(d, 2H, J=12.0Hz), 7.61(d, 2H, J=12.0Hz), 7.83-7.86(m, 4H), 7.82(s, 1H)	DMSO-d6, 400
2-218		212	1.32-1.54(m, 4H), 1.60(s, 6H), 1.81-1.86(m, 2H), 2.05-2.10(m, 2H), 2.53-2.55(m, 1H), 3.05-3.18(m, 1H), 6.46(s, 2H), 6.54(d, 1H, J=8.0Hz), 6.84(bs, 2H), 7.31(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.85(s, 1H)	DMSO-d6, 300MHz

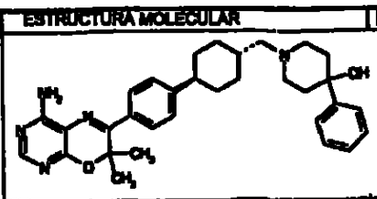
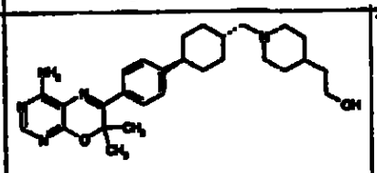
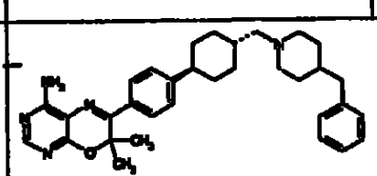
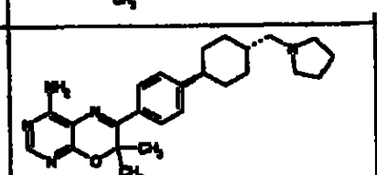
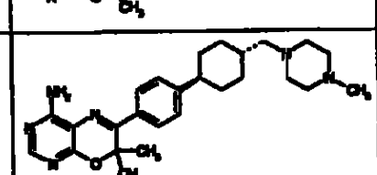
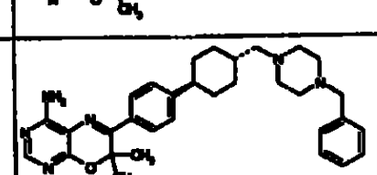
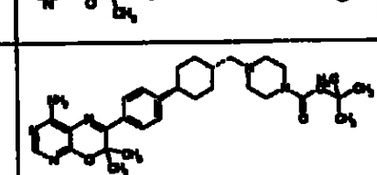
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-219		243- 249	1.08(s, 3H), 1.32(s, 3H), 1.44-1.62(m, 4H), 1.69-1.90(m, 4H), 2.45-2.69(m, 1H), 2.83-2.77(m, 1H), 2.81(s, 1.2H), 3.09(s, 1.8H), 4.11(s, 0.6H), 4.19(s, 0.4H), 6.26(s, 1H), 6.20(br, 2H), 7.26(d, 2H, J=8.1Hz), 7.37(d, 2H, J=8.1Hz), 7.61(s, 1H), 12.48(bs, 1H)	DMSO-d6, 400MHz
2-220		>250	1.16-1.28(m, 2H), 1.43-1.60(m, 2H), 1.61(s, 6H), 1.80-2.11(m, 6H), 2.53-2.69(m, 1H), 2.84(d, 2H, J=6.0Hz), 6.78(s, 2H), 6.93(brs, 2H), 7.31(d, 2H, J=8.0Hz), 7.66(d, 2H, J=8.0Hz), 7.86(s, 1H)	DMSO-d6, 300
2-221		>250	1.09(s, 3H), 1.15-1.27(m, 5H), 1.43-1.62(m, 2H), 1.80-2.08(m, 6H), 2.46-2.49(m, 1H), 2.83(d, 2H, J=6.0Hz), 4.11(brs, 1H), 6.25(brs, 1H), 6.20(brs, 2H), 6.76(s, 2H), 7.24(d, 2H, J=8.0Hz), 7.28(d, 2H, J=8.0Hz), 7.81(s, 1H)	DMSO-d6, 400
2-222		>250	1.07(s, 3H), 1.22(s, 3H), 1.24-1.65(m, 4H), 1.75-2.11(m, 4H), 2.41-2.48(m, 1H), 3.05-3.17(m, 1H), 4.11(brs, 1H), 6.25(brs, 1H), 6.21(brs, 2H), 6.45(brs, 2H), 6.55(d, 1H, J=12.0Hz), 7.34(d, 2H, J=8.0Hz), 7.39(d, 2H, J=8.0Hz), 7.80(s, 1H)	DMSO-d6, 300MHz
2-223			1.00-1.11(m, 6H), 1.22(s, 3H), 1.37-1.48(m, 2H), 1.77-1.88(m, 4H), 2.43-2.46(m, 1H), 3.24-3.37(m, 2H), 4.11(brs, 1H), 4.30-4.33(m, 1H), 5.25(brs, 1H), 6.20(brs, 2H), 7.24(d, 2H, J=8.0Hz), 7.39(d, 2H, J=8.0Hz), 7.81(s, 1H)	DMSO-d6, 400
2-224		168 - 171	0.94-1.06(m, 2H), 1.36-1.60(m, 16H), 1.76-1.93(m, 4H), 2.03-2.13(m, 2H), 2.25-2.35(m, 3H), 2.62-2.66(m, 1H), 6.81(brs, 2H), 7.30(d, 2H, J=12.0Hz), 7.84(d, 2H, J=12.0Hz), 7.94(s, 1H)	DMSO-d6, 400
2-225			0.83-1.06(m, 2H), 1.36-2.16(m, 21H), 2.63-2.66(m, 1H), 2.84-2.72(m, 2H), 3.39-3.48(m, 1H), 4.47-4.51(m, 1H), 6.81(brs, 2H), 7.30(d, 2H, J=8.0Hz), 7.84(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 300

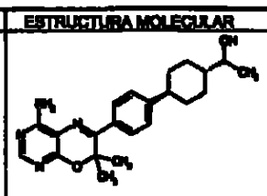
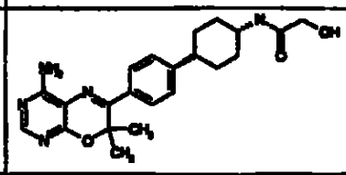
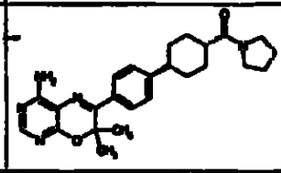
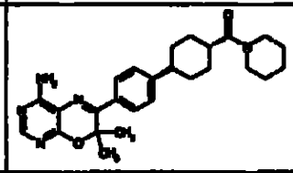
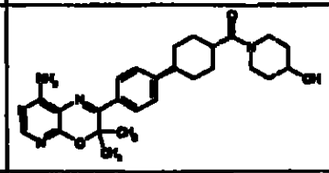
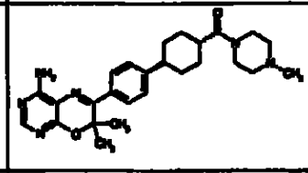
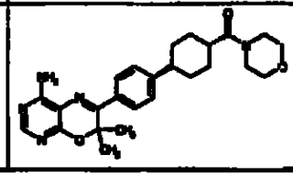
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-226			0.97-1.11(m, 2H), 1.40-1.58(m, 11H), 1.79-2.01(m, 7H), 2.18-2.31(m, 2H), 2.39-2.47(m, 2H), 2.63-2.74(m, 2H), 4.76(bra, 1H), 6.92(bra, 2H), 7.18-7.36(m, 6H), 7.49(d, 2H, J=8.0Hz), 7.85(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-227		196 - 200	0.91-1.89(m, 21H), 1.77-1.94(m, 4H), 2.05-2.16(m, 1H), 2.53-2.61(m, 1H), 2.74-2.89(m, 2H), 3.40-3.46(m, 2H), 4.30(bra, 1H), 6.91(bra, 2H), 7.30(d, 2H, J=8.0Hz), 7.85(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-228		119 - 120	0.91-1.85(m, 18H), 1.78-1.90(m, 6H), 2.11(bra, 1H), 2.85-2.59(m, 1H), 2.72-2.91(m, 2H), 6.91(bra, 2H), 7.15-7.33(m, 7H), 7.84(d, 2H, J=8.0Hz), 7.96(s, 1H)	DMSO-d6, 300
2-229		160 - 162	0.97-1.11(m, 2H), 1.39-1.97(m, 18H), 2.27-2.63(m, 3H), 3.24(bra, 2H), 6.91(bra, 2H), 7.30(d, 2H, J=8.0Hz), 7.84(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-230			0.91-1.10(m, 2H), 1.37-1.83(m, 11H), 1.78-1.83(m, 6H), 2.08-2.43(m, 10H), 2.52-2.59(m, 1H), 6.91(bra, 2H), 7.30(d, 2H, J=8.0Hz), 7.84(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-231			0.85-1.07(m, 2H), 1.37-1.85(m, 11H), 1.78-1.91(m, 4H), 2.15-2.23(m, 2H), 2.32-2.47(m, 6H), 3.45-3.51(m, 2H), 6.91(bra, 2H), 7.25-7.35(m, 7H), 7.84(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 300
2-232		171 - 172	0.95-1.09(m, 2H), 1.39(s, 6H), 1.41-1.51(m, 2H), 1.80(s, 6H), 1.80-1.91(m, 6H), 2.13(bra, 2H), 2.39-2.33(m, 4H),2.46-2.53(m, 4H), 2.53-2.57(m, 1H), 6.90(bra, 2H), 7.39(d, 2H, J=8.0Hz), 7.83(d, 2H, J=8.0Hz), 7.95(s, 1H)	DMSO-d6, 400MHz

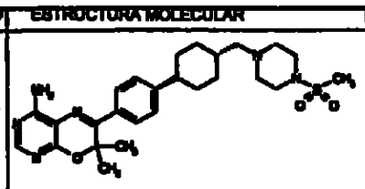
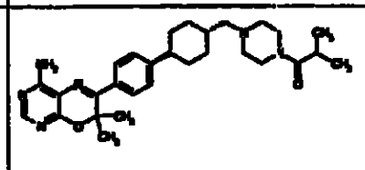
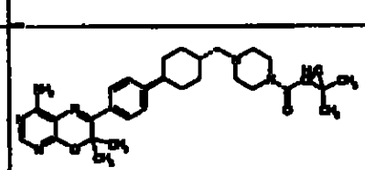
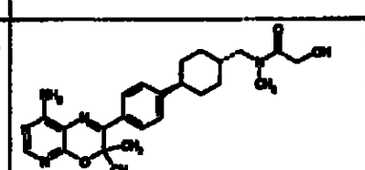
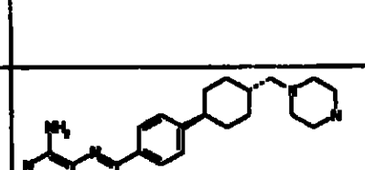
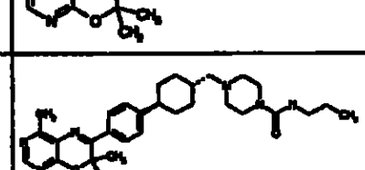
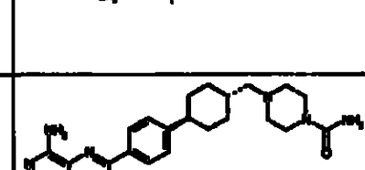
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F	NMR(δ)	SOLVENTE
2-233		224 - 229	1.09(d, 3H, J=6.6Hz), 1.06-1.31(m, 3H), 1.38-1.52(m, 2H), 1.61(s, 6H), 1.71-1.83(m, 1H), 1.90-1.93(m, 2H), 2.01-2.47(m, 1H), 2.37-3.46(m, 1H), 6.92(br, 2H); 7.30(d, 2H, J=8.4Hz), 7.84(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 400MHz
2-234		228 - 230	1.37-1.57(m, 4H), 1.61(s, 6H), 1.78-1.92(m, 4H), 2.46-2.60(m, 1H), 3.62-3.78(m, 1H), 3.75(s, 2H), 6.93(br, 2H), 7.33(d, 2H, J=8.4Hz), 7.48(d, 1H, J=8.4Hz), 7.85(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-235		201 - 202	1.48-1.66(m, 4H), 1.61(s, 6H), 1.71-1.93(m, 6H), 2.43-2.63(m, 2H), 3.35-3.53(m, 2H), 3.43-3.64(m, 2H), 6.93(br, 2H), 7.31(d, 2H, J=8.4Hz), 7.85(d, 2H, J=8.4Hz), 7.96(s, 1H)	DMSO-d6, 300MHz
2-236		220 - 224	1.33-1.66(m, 14H), 1.61(s, 6H), 2.51(s, 2H), 3.38(s, 4H), 6.92(br, 2H), 7.31(d, 2H, J=8.1Hz), 7.85(d, 2H, J=8.1Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-237		250 - 252	1.16-1.36(m, 2H), 1.46-1.62(m, 8H), 1.61(s, 6H), 2.51-2.61(m, 2H), 2.67-3.00(m, 1H), 3.12-3.25(m, 1H), 3.62-3.86(m, 4H), 4.54-4.76(m, 1H), 6.93(br, 2H), 7.31(d, 2H, J=8.4Hz), 7.85(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-238		190 - 191	1.48-1.66(m, 4H), 1.61(s, 6H), 1.72-1.92(m, 4H), 2.30(s, 3H), 2.32-2.36(m, 4H), 2.51-2.75(m, 2H), 2.41-3.55(m, 4H), 6.93(br, 2H), 7.31(d, 2H, J=8.4Hz), 7.85(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-239		233 - 235	1.47-1.57(m, 4H), 1.57(s, 6H), 1.79-1.92(m, 4H), 2.47-2.77(m, 2H), 3.37-3.65(m, 8H), 6.92(br, 2H), 7.31(d, 2H, J=8.4Hz), 7.85(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz

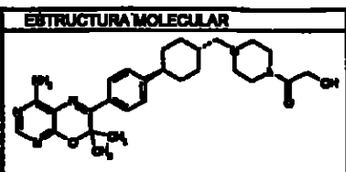
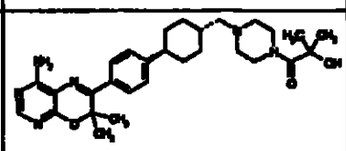
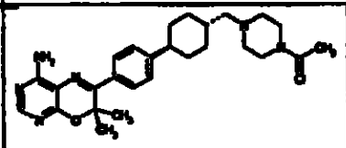
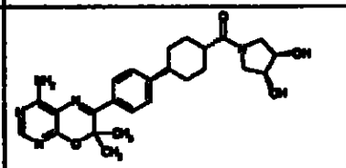
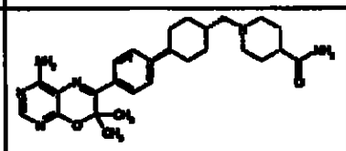
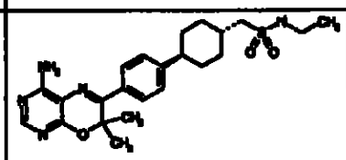
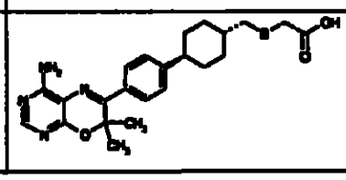
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Tabla 2 (Continuación)

NÚMERO DE EJEMPLO	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-240		233 - 235	0.85-1.09(m, 2H), 1.27-1.58(m, 3H), 1.60(s, 6H), 1.77-1.96(m, 4H), 2.19(brd, 2H, J=7.0Hz), 2.38-2.48(m, 4H), 2.53-2.61(m, 1H), 3.07-3.14(m, 4H), 6.91(br, 2H), 7.30(d, 2H, J=8.4Hz), 7.84(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-241		120 - 128	0.98-1.10(m, 2H), 0.99(d, 6H, J=6.6Hz), 1.41-1.55(m, 3H), 1.60(s, 6H), 1.81-1.93(m, 4H), 2.15(brd, 2H, J=7.0Hz), 2.27-2.35(m, 4H), 2.48-2.59(m, 1H), 2.80-2.89(m, 1H), 3.40-3.51(m, 4H), 6.93(br, 2H), 7.30(d, 2H, J=8.4Hz), 7.84(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
2-242		171 - 172	0.98-1.08(m, 2H), 1.39(s, 9H), 1.41-1.51(m, 3H), 1.60(s, 6H), 1.80-1.91(m, 6H), 2.13(brs, 2H), 2.28-2.32(m, 4H),2.48-2.53(m, 4H), 2.82-2.87(m, 1H), 6.90(brs, 2H), 7.28(d, 2H, J=8.0Hz), 7.83(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-243		208 - 210	a mixture of 2 conformers: 1.02-1.13(m, 2H), 1.38-1.58(m, 2H), 1.59(s, 6H), 1.81-1.91(m, 6H), 2.51(m, 1H), 2.85 and 2.87(s, 3H), 3.09 and 3.20(d, 2H, J=6.8 Hz), 4.06 and 4.07(brs, 2H), 4.30 and 4.35(brs, 1H), 6.91(brs, 2H), 7.27(d, 2H, J=8.3 Hz), 7.81(d, 2H, J=8.3 Hz), 7.92(s, 1H).	DMSO-d6, 400MHz
2-244		208 - 209	0.94-1.05(m, 2H), 1.41-1.60(m, 2H), 1.60(s, 6H), 1.75-1.90(m, 5H), 2.08(d, 2H, J=6.6Hz), 2.33-2.39(m, 4H), 2.69-2.71(m, 4H), 6.93(brs, 2H), 7.28(d, 2H, J=8.6Hz), 7.82(d, 2H, J=8.6Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-245		160 - 162	0.83(t, 3H, J=7.4 Hz), 1.04-1.13(m, 2H), 1.37-1.58(m, 6H), 1.60(s, 6H), 1.80-1.90(m, 4H), 2.01-2.15(m, 2H), 2.19-2.39(m, 4H), 2.91(m, 1H), 2.95(q, 2H, J=7.4 Hz), 3.30-3.38(m, 4H), 6.40(brs, 1H), 6.91(brs, 2H), 7.28(d, 2H, J=8.3 Hz), 7.82(d, 2H, J=8.3 Hz), 7.93(s, 1H).	DMSO-d6, 400MHz
2-246		156 - 160	1.04-1.13(m, 2H), 1.37-1.58(m, 2H), 1.59(s, 6H), 1.80-1.90(m, 4H), 2.01-2.15(m, 2H), 2.19-2.39(m, 4H), 2.91(m, 1H), 3.30-3.38(m, 4H), 5.89(brs, 2H), 6.91(brs, 2H), 7.27(d, 2H, J=8.3 Hz), 7.81(d, 2H, J=8.3 Hz), 7.92(s, 1H).	DMSO-d6, 400MHz

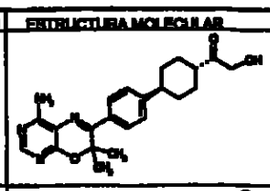
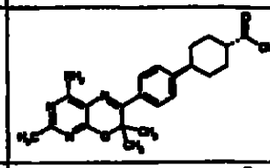
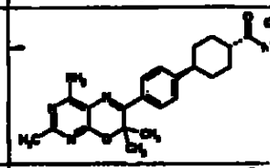
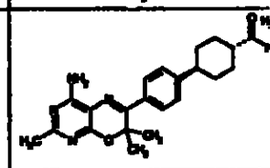
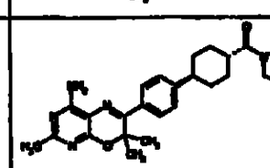
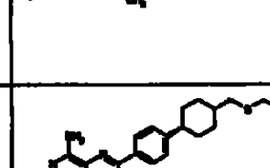
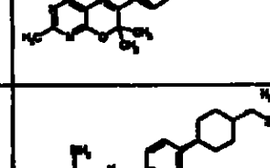
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-247		205 - 206	0.98-1.07(m, 2H), 1.43-1.51(m, 2H), 1.60(s, 6H), 1.80-1.92(m, 6H), 2.14(d, 2H, J=6.0Hz), 2.28-2.39(m, 4H), 2.62-2.69(m, 1H), 3.43-3.48(m, 4H), 4.07(d, 2H, J=6.0Hz), 4.23(t, 1H, J=6.0Hz), 6.83(brs, 2H), 7.26(d, 2H, J=8.6Hz), 7.53(d, 2H, J=8.0Hz), 7.82(s, 1H)	DMSO-d6, 400MHz
2-248		207 - 208	1.00-1.04(m, 2H), 1.30(s, 6H), 1.40-1.52(m, 2H), 1.60(s, 6H), 1.75-1.83(m, 2H), 2.12(d, 2H, J=6.0Hz), 2.30-2.38(m, 4H), 2.63-2.68(m, 1H), 3.76-3.97(m, 4H), 6.82(brs, 2H), 7.26(d, 2H, J=8.6Hz), 7.53(d, 2H, J=12.8Hz), 7.82(s, 1H)	DMSO-d6, 400MHz
2-249		202 - 203	0.97-1.06(m, 2H), 1.43-1.50(m, 2H), 1.60(s, 6H), 1.81-1.92(m, 6H), 1.98(s, 3H), 2.14(d, 2H, J=6.0Hz), 2.28-2.39(m, 4H), 2.62-2.68(m, 1H), 3.38-3.45(m, 4H), 6.83(brs, 2H), 7.26(d, 2H, J=8.6Hz), 7.53(d, 2H, J=12.0Hz), 7.82(s, 1H)	DMSO-d6, 400MHz
2-250		220 - 240	1.43-1.58(m, 4H), 1.61(s, 6H), 1.73-1.92(m, 4H), 2.38-2.64(m, 2H), 3.13-3.41(m, 3H), 3.65(dd, 1H, J=8.9, 8.9Hz), 3.96-4.11(m, 2H), 4.66(br, 1H), 4.82(br, 1H), 6.83(br, 2H), 7.32(d, 2H, J=8.4Hz), 7.58(d, 2H, J=8.4Hz), 7.85(s, 1H)	DMSO-d6, 300MHz
2-251		169 - 184	.00(m, 2H), 1.39-1.72(m, 8H), 1.80(s, 6H), 1.77-1.93(m, 6H), 1.97-2.16(m, 2H), 2.45-2.61(m, 1H), 2.76-2.89(m, 1H), 6.87(br, 1H), 6.91(br, 2H), 7.17(br, 1H), 7.30(d, 2H, J=8.1Hz), 7.64(d, 2H, J=8.1Hz), 7.86(s, 1H)	DMSO-d6, 300MHz
2-252		209 - 211	1.04(t, 3H, J=7.4 Hz), 1.20-1.28(m, 2H), 1.45-1.58(m, 2H), 1.60(s, 6H), 1.80-1.89(m, 4H), 2.01-2.07(m, 2H), 2.61(m, 1H), 2.82-3.01(m, 4H), 6.80(brs, 1H), 7.06(brt, 1H, J=5.6 Hz), 7.28(d, 2H, J=8.3 Hz), 7.63(d, 2H, J=8.3 Hz), 7.84(s, 1H).	DMSO-d6, 400MHz
2-253		248(dec.)	1.08-1.17(m, 2H), 1.38-1.64(m, 6H), 1.78-1.88(m, 4H), 2.62(t, 2H, J=6.0Hz), 3.22(s, 2H), 3.30(s, 2H), 6.82(brs, 2H), 7.30(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 7.85(s, 1H), 12.40(brs, 1H)	DMSO-d6, 300

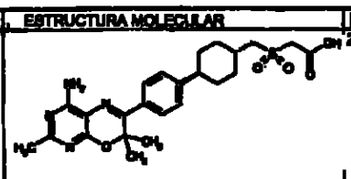
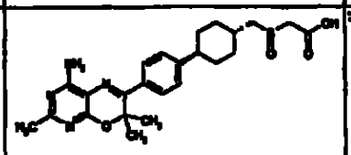
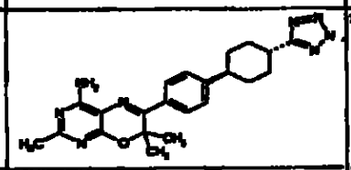
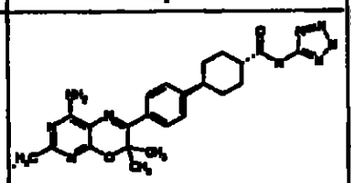
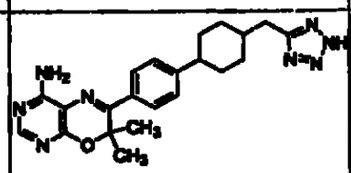
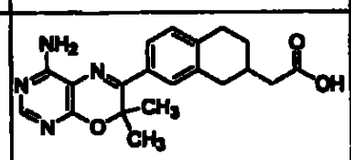
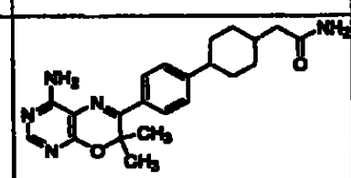
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(A)	SOLVENTE
2-254		213 - 214	1.39-1.52(m, 4H), 1.60(s, 6H), 1.85-1.93(m, 4H), 2.62-2.69(m, 2H), 4.16(brm, 2H), 4.57(brm, 1H), 6.93(brs, 2H), 7.28(d, 2H, J=8.0Hz), 7.63(d, 2H, J=8.0Hz), 7.93(s, 1H)	DMSO-d6, 400MHz
2-255		>250	1.44-1.53(m, 4H), 1.59(s, 6H), 1.83-1.89(m, 2H), 1.89-2.03(m, 2H), 2.24(s, 3H), 2.39(brm, 1H), 6.84(brs, 2H), 7.30(d, 2H, J=8.0Hz), 7.63(d, 2H, J=8.0Hz), 12.05(brs, 1H)	DMSO-d6, 300MHz
2-256		172 - 175	1.43-1.55(m, 4H), 1.59(s, 6H), 1.84-1.97(m, 4H), 2.24(s, 3H), 2.39-2.53(m, 1H), 2.73(brs, 1H), 3.53(brs, 3H), 7.30(d, 2H, J=8.0Hz), 7.63(d, 2H, J=8.0Hz), 11.57(brs, 1H)	DMSO-d6, 300MHz
2-257		220 - 225	1.19(s, 6H), 1.39-1.55(m, 4H), 1.59(s, 6H), 1.76-1.87(m, 4H), 2.15-2.33(m, 1H), 2.24(s, 3H), 2.55-2.59(m, 1H), 3.57(d, 2H, J=5.0Hz), 4.30(t, 1H, J=5.0Hz), 6.83(br, 2H), 7.18(brs, 1H), 7.29(d, 2H, J=8.0Hz), 7.63(d, 2H, J=8.0Hz)	DMSO-d6, 300MHz
2-258		>250	1.44-1.61(m, 4H), 1.59(s, 6H), 1.75-1.88(m, 4H), 2.26(s, 3H), 2.41-2.51(m, 2H), 2.54-2.63(m, 1H), 3.19(dd, 1H, J=12.0, 6.0Hz), 3.37(dd, 1H, J=12.0, 6.0Hz), 3.65(dd, 1H, J=8.0, 6.0Hz), 3.99-4.03(m, 1H), 4.09-4.16(m, 1H), 4.67(d, 1H, J=6.0Hz), 4.99(d, 1H, J=6.0Hz), 6.83(br, 1H), 7.31(d, 2H, J=8.0Hz), 7.63(d, 2H, J=8.0Hz)	DMSO-d6, 300MHz
2-259		271 - 277	1.05- 1.20 (m, 2 H), 1.36- 1.62 (m, 3 H), 1.58 (s, 6 H), 1.77- 1.98 (m, 4 H), 2.24 (s, 3 H), 2.47- 2.68 (m, 1 H), 2.84 (d, J = 8.0 Hz, 2 H), 3.31 (s, 2 H), 6.81 (br s, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 7.62 (d, J = 8.0 Hz, 2 H), 12.48 (s, 1 H).	DMSO-d6, 300 MHz
2-260		235-239	1.01- 1.21 (m, 2 H), 1.33- 1.54 (m, 3 H), 1.41 (s, 6 H), 1.58 (s, 6 H), 1.77- 1.97 (m, 4 H), 2.24 (s, 3 H), 2.43- 2.61 (m, 3 H), 6.83 (br s, 2 H), 7.28 (d, J = 8.2 Hz, 2 H), 7.61 (d, J = 8.2 Hz, 2 H), 12.49 (br s, 1 H).	DMSO-d6, 300 MHz

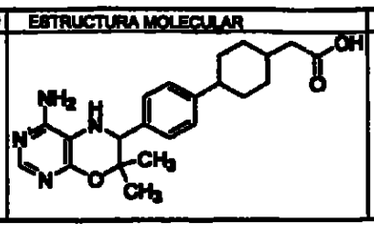
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-281		226-227	1.17- 1.36 (m, 2 H), 1.44- 1.66 (m, 2 H), 1.55 (s, 6 H), 1.77- 1.86 (m, 2 H), 1.89- 2.15 (m, 3 H), 2.35 (s, 3 H), 2.45- 2.62 (m, 1 H), 2.37 (d, J = 8.0 Hz, 2 H), 4.26 (s, 2 H), 6.61 (br s, 2 H), 7.30 (d, J = 8.2 Hz, 2 H), 7.62 (d, J = 8.2 Hz, 2 H), 12.26 (br s, 1 H).	DMSO-d6, 300 MHz
2-282		>166	1.18- 1.37 (m, 2 H), 1.48- 1.64 (m, 2 H), 1.55 (s, 6 H), 1.79- 1.94 (m, 4 H), 1.98- 2.09 (m, 1 H), 2.34 (s, 3 H), 2.44- 2.61 (m, 1 H), 2.64- 2.74 (m, 1 H), 2.81- 2.89 (m, 1 H), 3.09 (d, J = 14.1 Hz, 1 H), 3.82 (d, J = 14.1 Hz, 1 H), 6.60 (br s, 2 H), 7.29 (d, J = 8.4 Hz, 2 H), 7.61 (d, J = 8.4 Hz, 2 H), 12.05 (s, 1 H).	DMSO-d6, 400 MHz
2-283		>250	1.55(s, 6H), 1.51-1.75(m, 4H), 1.89-1.99(m, 2H), 2.10-2.21(m, 2H), 2.35(s, 3H), 2.67(br, 1H), 3.09(br, 1H), 6.53(br, 2H), 7.36(d, 2H, J=8.0Hz), 7.69(d, 2H, J=8.0Hz), 12.07(bra, 1H)	DMSO-d6, 300MHz
2-284		>250	1.44-1.69(m, 4H), 1.55(s, 6H), 1.89-1.94(m, 2H), 2.00-2.04(m, 2H), 2.25(s, 3H), 2.55-2.66(m, 2H), 3.10-3.19(m, 2H), 6.53(br, 1H), 7.33(d, 2H, J=8.0Hz), 7.64(d, 2H, J=8.0Hz), 11.99(br, 1H)	DMSO-d6, 300MHz
2-285				
2-286				
2-287				

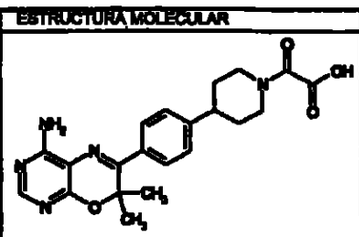
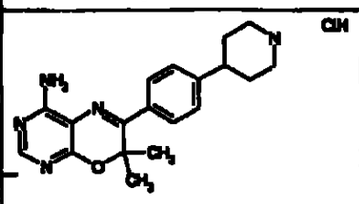
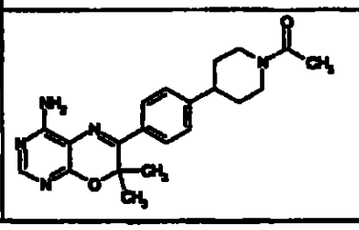
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Tabla 2 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
2-288				

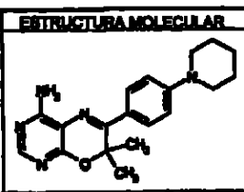
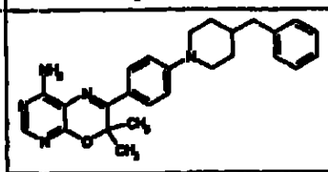
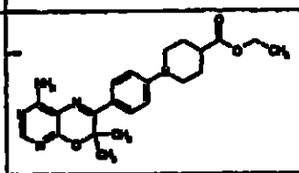
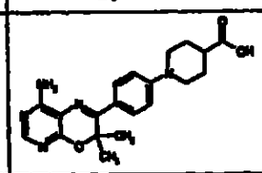
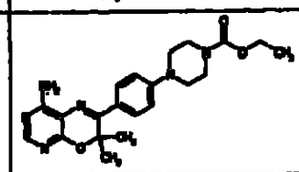
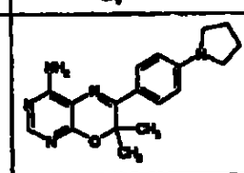
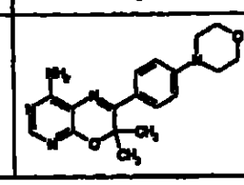
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Tabla 3

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
3		188 - 190	1.48-1.82(m, 2H), 1.60(s, 6H), 1.81-1.94(m, 2H), 2.73-2.99(m, 2H), 3.22-3.34(m, 1H), 3.63-3.70(m, 1H), 4.33-4.44(m, 1H), 7.00(br, 2H), 7.33(d, 2H, J=8.4Hz), 7.57(d, 2H, J=8.4Hz), 7.95(s, 1H)	DMSO-d6, 300MHz
3-2			1.63(s, 6H), 1.76-2.02(m, 4H), 2.69-3.11(m, 3H), 3.33-3.47(m, 2H), 7.24(br, 2H), 7.32(d, 2H, J=8.1Hz), 7.73(d, 2H, J=8.1Hz), 8.04(s, 1H), 8.69(br, 1H)	DMSO-d6, 300MHz
3-3		232 - 237	1.39-1.84(m, 2H), 1.60(s, 6H), 1.73-1.84(m, 2H), 2.04(s, 3H), 2.64-2.84(m, 1H), 2.77-2.90(m, 1H), 3.07-3.20(m, 1H), 3.87-3.99(m, 1H), 4.48-4.60(m, 1H), 6.95(br, 2H), 7.33(d, 2H, J=8.4Hz), 7.66(d, 2H, J=8.4Hz), 7.99(s, 1H)	DMSO-d6, 300MHz

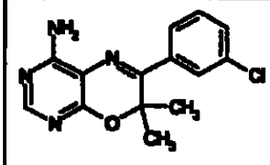
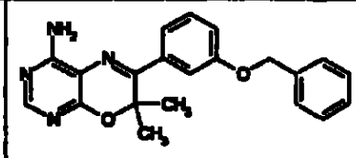
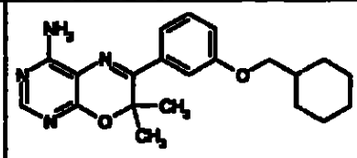
3/2

Tabla 4

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	RMN(δ)	SOLVENTE
4		191 - 193	1.58-1.63(m, 6H), 1.83(s, 6H), 3.28(bs, 4H), 6.79(bs, 2H), 7.39(d, 2H, J=8.8 Hz), 7.63(d, 2H, J=8.8 Hz), 7.91(s, 1H).	DMSO-d6, 400MHz
4-2			1.21-1.30(m, 2H), 1.82(s, 6H), 1.61-1.80(m, 3H), 2.54(d, 2H, J=7.0 Hz), 2.73(bd, 2H, J=12.8 Hz), 3.53(bd, 2H, J=12.8 Hz), 6.79(bs, 2H), 6.91(d, 2H, J=8.8 Hz), 7.17-7.31(m, 5H), 7.62(d, 2H, J=8.8 Hz), 7.91(s, 1H).	DMSO-d6, 400MHz
4-3		175 - 177	1.18(t, 3H, J=6.0Hz), 1.67-1.89(m, 6H), 1.85-1.93(m, 2H), 2.54-2.61(m, 1H), 2.68-2.83(m, 2H), 3.76-3.83(m, 2H), 4.09(q, 2H, J=7.0Hz), 6.87(bs, 2H), 6.98(d, 2H, J=8.8Hz), 7.86(d, 2H, J=8.8Hz), 7.92(s, 1H)	DMSO-d6, 300
4-4		>240	1.57-1.89(m, 6H), 1.87-1.93(m, 2H), 2.46-2.47(m, 1H), 2.67-2.83(m, 2H), 3.76-3.80(m, 2H), 6.82(bs, 2H), 6.94(d, 2H, J=8.8Hz), 7.84(d, 2H, J=8.8Hz), 7.91(s, 1H)	DMSO-d6, 400
4-5		174 - 175	1.21(t, 3H, J=6.8Hz), 1.83(s, 6H), 2.23-3.27(m, 2H), 3.50-3.53(m, 2H), 4.09(q, 2H, J=6.7Hz), 6.82(bs, 2H), 6.97(d, 2H, J=12.8Hz), 7.86(d, 2H, J=8.8Hz), 7.92(s, 1H)	DMSO-d6, 400
4-6		191 - 196	1.83(s, 6H), 1.86-1.98(m, 4H), 3.25-3.31(m, 4H), 6.85(d, 2H, J=8.8Hz), 6.77(bs, 2H), 7.55(d, 2H, J=8.8Hz), 7.90(s, 1H)	DMSO-d6, 400MHz
4-7		214 - 219	1.82(s, 6H), 3.22(t, 4H, J=4.8Hz), 3.76(t, 4H, J=4.8Hz), 6.82(br, 2H), 6.86(d, 2H, J=8.4Hz), 7.57(d, 2H, J=8.4Hz), 7.92(s, 1H)	DMSO-d6, 400MHz

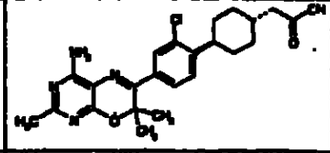
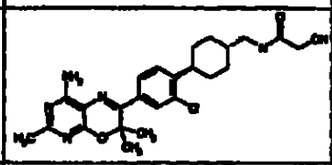
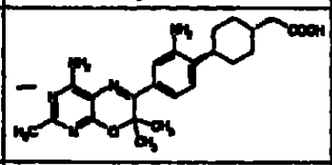
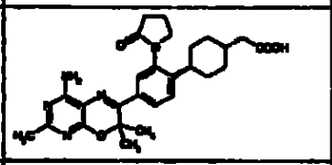
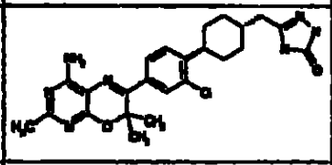
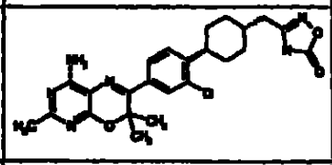
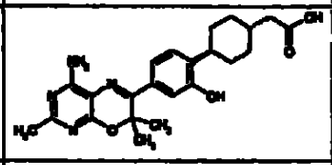
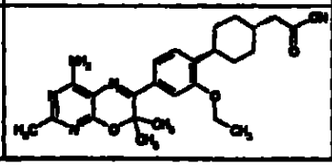
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Tabla 5

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
5		117 - 133	1.60(s, 6H), 7.01(br, 2H), 7.48(t, 1H, J=8.1Hz), 7.58(ddd, 1H, J=1.0, 2.0, 1.0Hz), 7.67(dt, 1H, J=8.1, 1.0Hz), 7.76(t, 1H, J=2.0Hz), 7.97(s, 1H)	DMSO-d6, 400MHz
5-2		130 - 131	1.59(s, 6H), 5.20(s, 2H), 6.93(br, 2H), 7.15(d, 1H, J=8.2Hz), 7.35-7.49(m, 6H), 7.97(s, 1H)	DMSO-d6, 400MHz
5-3		161 - 162	1.03-1.33(m, 5H), 1.60(s, 6H), 1.65-1.88(m, 6H), 3.85(d, 2H, J=6.2Hz), 6.94(br, 2H), 7.08(dd, 1H, J=2.5, 8.0Hz), 7.17(d, 1H, J=2.5Hz), 7.23(d, 1H, J=8.0Hz), 7.25(t, 1H, J=8.0Hz), 7.97(s, 1H)	DMSO-d6, 400MHz

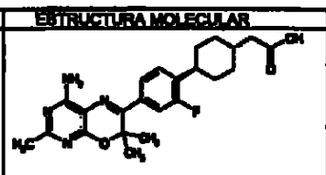
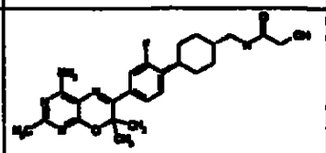
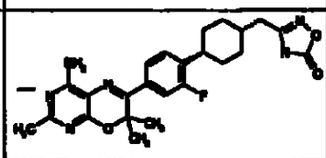
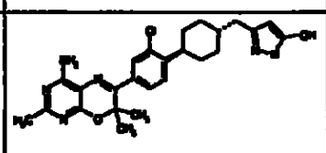
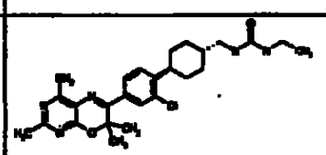
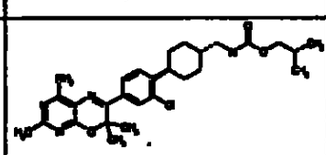
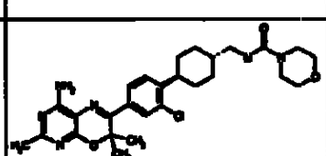
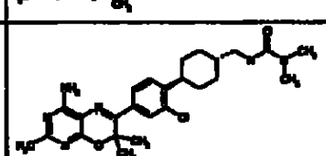
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Tabla 6

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
6		>230	1.05-1.22(m, 2H), 1.41-1.55(m, 2H), 1.55(s, 6H), 1.70-1.91(m, 6H), 2.10(d, 2H, J=6.7 Hz), 2.24(s, 3H), 2.52(m, 1H), 6.91(brs, 2H), 7.42(d, 1H, J=8.1 Hz), 7.62(dd, 1H, J=8.1, 1.8 Hz), 7.72(d, 1H, J=1.8 Hz), 12.15(brs, 1H).	DMSO-d6, 400MHz
6-2		229 - 232	0.95- 1.16 (m, 2 H), 1.34- 1.64 (m, 3 H), 1.55 (s, 6 H), 1.70- 1.89 (m, 4 H), 2.24 (s, 3 H), 2.83- 2.95 (m, 1 H), 3.02 (t, J = 6.8 Hz, 1 H), 3.81 (s, 2 H), 6.42 (br s, 1 H), 6.91 (br s, 2 H), 7.41 (d, J = 8.3 Hz, 1 H), 7.63 (d, J = 8.3 Hz, 1 H), 7.65- 7.72 (m, 1 H), 7.73 (s, 1 H).	DMSO-d6, 300 MHz
6-3		260(dec.)	1.18-1.42(m, 6H), 1.58(s, 6H), 1.80(m, 4H), 2.22(s, 3H), 2.15(d, 2H, J=6.6Hz), 4.57(bs, 2H), 6.75(brs, 2H), 6.82(dd, 1H, J=8.3Hz, 1.8Hz), 6.93(d, 1H, J=1.8Hz), 7.01(d, 1H, J=8.3Hz).	DMSO-d6, 300MHz
6-4		177(dec.)	1.01-1.08(m, 2H), 1.45-1.58(m, 2H), 1.56(s, 6H), 1.70-1.83(m, 6H), 2.13-2.19(m, 4H), 2.25(s, 3H), 2.41-2.48(m, 2H), 3.83-3.89(m, 2H), 6.87(brs, 2H), 7.42(d, 1H, J=8.3Hz), 7.51(d, 1H, J=1.8Hz), 7.63(dd, 1H, J=8.3, 1.8Hz).	DMSO-d6, 300MHz
6-5		>300	1.15- 1.25 (m, 2 H), 1.37- 1.57 (m, 2 H), 1.59 (s, 6 H), 1.65- 1.84 (m, 6 H), 2.24 (s, 3 H), 2.31 (d, J = 6.6 Hz, 2 H), 2.85- 3.01 (m, 1 H), 6.89 (s, 2 H), 7.41 (d, J = 8.3 Hz, 1 H), 7.63 (dd, J = 1.8, 8.3 Hz, 1 H), 7.73 (d, J = 1.9 Hz, 1 H), 11.07 (s, 1 H), 11.77 (s, 1 H).	DMSO-d6, 300 MHz
6-6		>282	1.13- 1.32 (m, 2 H), 1.39- 1.57 (m, 2 H), 1.59 (s, 6 H), 1.78- 1.88 (m, 6 H), 2.25 (s, 3 H), 2.46 (d, J = 6.8 Hz, 2 H), 2.87- 3.01 (m, 1 H), 6.91 (s, 2 H), 7.42 (d, J = 8.3 Hz, 1 H), 7.64 (dd, J = 1.8, 8.3 Hz, 1 H), 7.74 (d, J = 1.9 Hz, 1 H), 12.17 (s, 1 H).	DMSO-d6, 300 MHz
6-7		>250	1.03- 1.20 (m, 2 H), 1.33- 1.53 (m, 2 H), 1.59 (s, 6 H), 1.65- 1.89 (m, 6 H), 2.14 (d, J = 6.8 Hz, 2 H), 2.24 (s, 3 H), 2.75- 2.89 (m, 1 H), 6.77 (br s, 1 H), 7.07 (d, J = 7.9 Hz, 1 H), 7.08 (s, 1 H), 7.15 (d, J = 7.9 Hz, 1 H), 9.46 (s, 1 H), 11.89 (s, 1 H).	DMSO-d6, 300 MHz
6-8		224-226	1.03- 1.21 (m, 2 H), 1.31- 1.69 (m, 2 H), 1.35 (t, J = 6.9 Hz, 3 H), 1.59 (s, 6 H), 1.69- 1.89 (m, 5 H), 2.13 (d, J = 6.8 Hz, 2 H), 2.25 (s, 3 H), 2.78- 2.93 (m, 1 H), 4.10 (q, J = 6.9 Hz, 2 H), 6.83 (br s, 2 H), 7.17- 7.29 (m, 3 H), 11.88 (s, 1 H).	DMSO-d6, 300 MHz

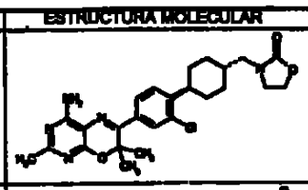
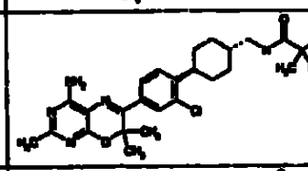
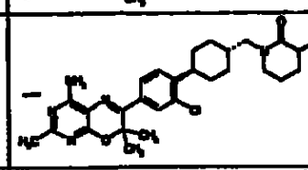
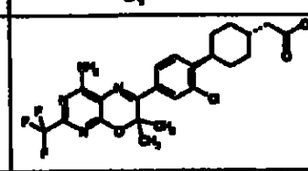
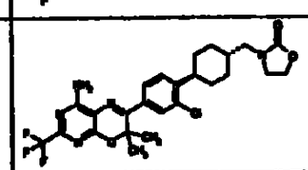
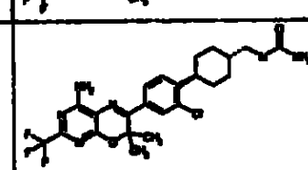
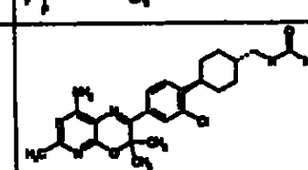
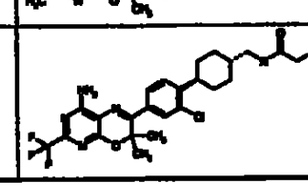
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Tabla 6 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
6-9		>250	1.07- 1.35 (m, 2 H), 1.44- 1.83 (m, 2 H), 1.89 (s, 6 H), 1.71- 1.90 (m, 5 H), 2.16 (d, J = 6.6 Hz, 2 H), 2.24 (s, 3 H), 2.70- 2.88 (m, 1 H), 6.88 (br s, 2 H), 7.24- 7.42 (m, 1 H), 7.48- 7.85 (m, 2 H), 12.02 (s, 1 H).	DMSO-d6, 300 MHz
6-10		212 - 214	1.01-1.14(m, 2H), 1.48-1.67(m, 2H), 1.89(s, 6H), 1.81(m, 4H), 2.24(s, 3H), 2.80(m, 1H), 3.03(m, 2H), 3.81(d, 2H, J=6.0Hz), 5.1(t, 1H, J=6.0Hz), 6.88(m, 2H), 7.24-7.40(m, 1H), 7.48-7.64(m, 2H), 7.67-7.71(m, 1H).	DMSO-d6, 300MHz
6-11		>282	1.15- 1.31 (m, 2 H), 1.42- 1.64 (m, 2 H), 1.89 (s, 6 H), 1.67- 1.88 (m, 5 H), 2.24 (s, 3 H), 2.44 (d, J = 6.8 Hz, 2 H), 2.75- 2.89 (m, 1 H), 6.89 (br s, 1 H), 7.33- 7.42 (m, 1 H), 7.47- 7.66 (m, 2 H), 12.18 (s, 1 H).	DMSO-d6, 300 MHz
6-12		171 - 173	1.05-1.19(m, 2H), 1.34-1.51(m, 2H), 1.89(s, 6H), 1.72-1.88(m, 4H), 2.24(s, 3H), 2.39(d, 2H, J=6.7 Hz), 2.82(m, 1H), 6.23(s, 1H), 6.90(bs, 2H), 7.40(d, 1H, J=8.1 Hz), 7.63(d, 1H, J=8.1Hz), 7.73(s, 1H), 8.30(bs, 1H), 11.20(bs, 1H).	DMSO-d6, 400MHz
6-13		>250	1.09(t, 3H, J=7.4 Hz), 1.03-1.19(m, 2H), 1.34-1.84(m, 2H), 1.89(s, 6H), 1.76-1.88(m, 4H), 2.25(s, 3H), 2.83-3.08(m, 6H), 6.79(t, 1H, J=5.8 Hz), 6.85(t, 1H, J=5.9 Hz), 6.88(bm, 2H), 7.43(d, 1H, J=8.1 Hz), 7.64(d, 1H, J=8.1Hz), 7.73(s, 1H).	DMSO-d6, 300MHz
6-14		205 - 209	0.88(d, 6H, J=6.6Hz), 1.01-1.13(m, 2H), 1.37-1.82(m, 2H), 1.89(s, 6H), 1.77-1.87(m, 6H), 2.25(s, 3H), 2.88(t, 2H, J=6.6Hz), 2.89-2.95(m, 1H), 3.73(d, 2H, J=6.6Hz), 6.85(br, 2H), 7.13(br, 1H), 7.42(d, 1H, J=8.0Hz), 7.63(dd, 1H, J=8.0, 3.0Hz), 7.73(d, 1H, J=3.0Hz)	DMSO-d6, 300MHz
6-15		225 - 228	1.00-1.11(m, 2H), 1.38-1.51(m, 2H), 1.89(s, 6H), 1.76-1.88(m, 4H), 2.24(s, 3H), 2.83-2.89(m, 2H), 3.34-3.37(m, 4H), 3.53-3.65(m, 4H), 6.83(t, 1H, J=6.6Hz), 6.85(br, 1H), 7.43(d, 1H, J=8.0Hz), 7.63(dd, 1H, J=8.0, 3.0Hz), 7.73(d, 1H, J=3.0Hz)	DMSO-d6, 300MHz
6-16		>250	0.86-1.10(m, 2H), 1.36-1.53(m, 2H), 1.89(s, 6H), 1.81-1.88(m, 4H), 2.25(s, 3H), 2.78(s, 6H), 2.89-2.94(m, 2H), 6.25(t, 1H, J=6.0Hz), 6.88(br, 2H), 7.43(d, 1H, J=8.0Hz), 7.63(dd, 1H, J=8.0, 3.0Hz), 7.73(d, 1H, J=3.0Hz)	DMSO-d6, 300MHz

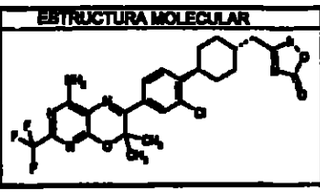
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Tabla 6 (Continuación)

NÚMERO EJEMPLO	ESTRUCTURA MOLECULAR	P.F.	RMN (δ)	SOLVENTE
6-17		>250	1.07-1.18(m, 2H), 1.45-1.64(m, 2H), 1.66(s, 6H), 1.64-1.74(m, 1H), 1.80-1.87(m, 4H), 2.25(s, 3H), 2.91-3.00(m, 1H), 3.08(d, 2H, J=6.0Hz), 3.86(t, 2H, J=6.0Hz), 4.27(t, 2H, J=6.0Hz), 6.92(br, 2H), 7.42(d, 1H, J=8.0Hz), 7.54(dd, 1H, J=8.0, 2.0Hz), 7.74(d, 1H, J=2.0Hz)	DMSO-d6, 300MHz
6-18		>250	0.95-1.18(m, 2H), 1.25(s, 6H), 1.38-1.63(m, 2H), 1.66(s, 6H), 1.77-1.89(m, 4H), 2.24(s, 3H), 2.86-2.98(m, 1H), 2.99(s, 2H, J=6.0Hz), 3.32(s, 1H), 3.86(br, 2H), 7.42(d, 1H, J=8.2Hz), 7.57-7.66(m, 2H), 7.73(d, 1H, J=1.5Hz)	DMSO-d6, 300MHz
6-19		225 - 228	1.05-1.18(m, 2H), 1.37-1.51(m, 2H), 1.56(s, 6H), 1.60-1.68(m, 1H), 1.71-1.87(m, 6H), 1.95-2.02(m, 1H), 2.24(s, 3H), 2.88-2.99(m, 1H), 3.09-3.18(m, 1H), 3.20-3.31(m, 4H), 3.85-3.91(m, 2H), 4.97(d, 1H, J=4.0Hz), 6.89(br, 2H), 7.40(d, 1H, J=8.0Hz), 7.62(d, 1H, J=8.0Hz), 7.73(s, 1H)	DMSO-d6, 400MHz
6-20		247 - 248	1.07-1.21(m, 2H), 1.44-1.52(m, 2H), 1.66(s, 6H), 1.70-1.80(m, 6H), 2.16(s, 3H, J=6.0Hz), 2.88-2.98(m, 1H), 7.46(d, 1H, J=8.0Hz), 7.48 and 7.53(brs, 2H), 7.60(dd, 1H, J=8.0, 4.0Hz), 7.80(d, 1H, J=4.0Hz), 12.04(brs, 1H)	DMSO-d6, 400MHz
6-21		>250	1.08-1.19(m, 2H), 1.41-1.55(m, 2H), 1.66(s, 6H), 1.68-1.73(m, 1H), 1.77-1.89(m, 4H), 2.91-3.01(m, 1H), 3.03(d, 2H, J=6.0Hz), 3.85(dd, 2H, J=8.0, 6.0Hz), 4.27(dd, 2H, J=8.0, 6.0Hz), 7.44(d, 1H, J=8.0Hz), 7.71(dd, 1H, J=8.0, 2.0Hz), 7.82(d, 1H, J=2.0Hz)	DMSO-d6, 300MHz
6-22		147(dec.)	1.01-1.14(m, 2H), 1.38-1.53(m, 2H), 1.66(s, 6H), 1.76-1.88(m, 4H), 2.88(t, 1H, J=6.0Hz), 2.89-2.99(m, 2H), 6.34(brs, 2H), 6.88(t, 1H, J=4.8Hz), 7.46(d, 1H, J=8.0Hz), 7.70(dd, 1H, J=8.0, 2.0Hz), 7.81(d, 1H, J=2.0Hz)	DMSO-d6, 300MHz
6-23		160 - 168	0.99-1.13(m, 2H), 1.38-1.51(m, 2H), 1.66(s, 6H), 1.76-1.88(m, 4H), 2.28(s, 3H), 2.88-3.01(m, 1H), 2.89(t, 2H, J=6.6Hz), 6.34(s, 2H), 6.88(t, 1H, J=6.6Hz), 6.89(br, 2H), 7.42(d, 1H, J=8.2Hz), 7.62(dd, 1H, J=1.8, 8.2Hz), 7.73(d, 1H, J=1.8Hz)	DMSO-d6, 300MHz
6-24		213 - 218	0.98-1.16(m, 2H), 1.33-1.62(m, 2H), 1.66(s, 6H), 1.77-1.89(m, 4H), 2.87-2.98(m, 1H), 3.03(d, 2H, J=6.0Hz), 3.81(d, 2H, J=6.0Hz), 5.43(t, 1H, J=6.0Hz), 7.44(d, 1H, J=8.2Hz), 7.62(br, 1H), 7.68-7.73(m, 1H), 7.69(d, 1H, J=8.2Hz), 7.76(br, 1H), 7.81(s, 1H)	DMSO-d6, 300MHz

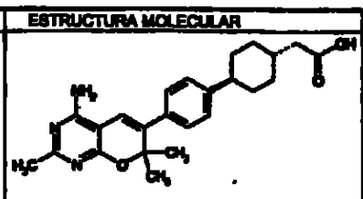
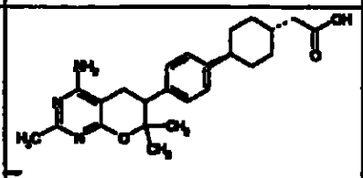
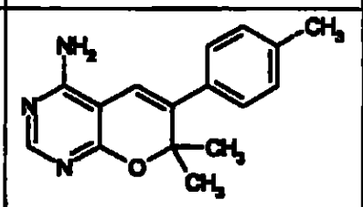
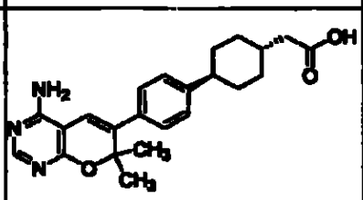
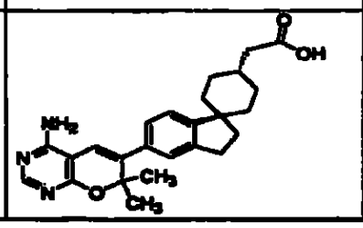
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Tabla 6 (Continuación)

NÚMERO EJEMPLO	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
6 [illegible]		226 - 227	1.16-1.26(m, 2H), 1.43-1.53(m, 2H), 1.56(s, 6H), 1.73-1.87(m, 6H), 2.44(d, 2H, J=6.0Hz), 2.53-2.65(m, 1H), 7.43(d, 1H, J=8.0Hz), 7.68(dd, 1H, J=8.0, 4.0Hz), 7.81(d, 1H, J=4.0Hz)	CDCl3-d6, 400MHz

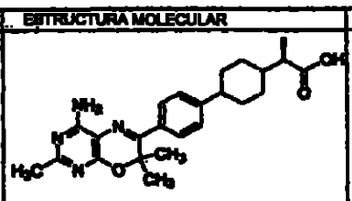
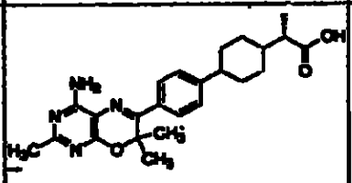
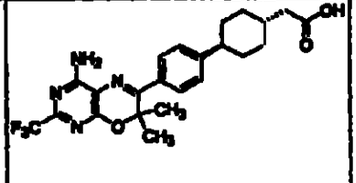
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Tabla 7

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
7		>228	1.04-1.19(m, 2H), 1.39-1.55(m, 2H), 1.49(s, 6H), 1.55-1.69(m, 6H), 2.14(d, 2H, J=7.2Hz), 2.21(s, 3H), 2.48-2.62(m, 1H), 6.55(s, 1H), 6.78(br, 2H), 7.23(d, 2H, J=8.2Hz), 7.27(d, 2H, J=8.2Hz), 12.01(s, 1H)	DMSO-d6, 300MHz
7-2			1.05-1.22(m, 2H), 1.13(s, 3H), 1.21(s, 3H), 1.39-1.52(m, 2H), 1.55-1.69(m, 6H), 2.14(d, 2H, J=6.6Hz), 2.30(s, 3H), 2.38-2.70(m, 3H), 2.89-3.04(m, 1H), 6.45(br, 2H), 7.18(d, 2H, J=8.2Hz), 7.22(d, 2H, J=8.2Hz), 11.89(brs, 1H)	DMSO-d6, 300MHz
7-3		>250	1.50(s, 6H), 2.33(s, 3H), 6.56(s, 1H), 6.66(br, 2H), 7.20(d, 2H, J=8.4Hz), 7.33(d, 2H, J=8.4Hz), 7.93(s, 1H)	DMSO-d6, 300MHz
7-4			8.09 (s, 1H), 7.23 (bs, 2H), 7.20 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 8.1 Hz, 2H), 6.61 (s, 1H), 2.47 (m, 1H), 2.16 (d, J = 6.9 Hz, 2H), 1.82 (m, 4H), 1.74 (m, 1H), 1.58 (s, 6H), 1.51 (m, 2H), 1.13 (m, 2H)	DMSO-d6, 400MHz
7-5			8.14 (s, 1H), 7.50 (bs, 2H), 7.20 (m, 3H), 6.61 (s, 1H), 2.56 (t, J = 7.2 Hz, 2H), 2.17 (d, J = 6.6 Hz, 2H), 1.85 (t, J = 7.3 Hz, 2H), 1.71 (m, 1H), 1.67 (m, 2H), 1.63 (m, 3H), 1.58 (s, 6H), 1.50 (m, 2H), 1.22 (m, 2H)	DMSO-d6, 400MHz

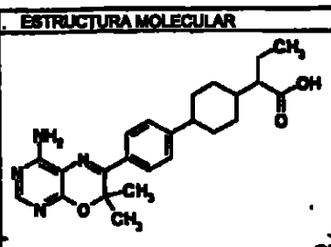
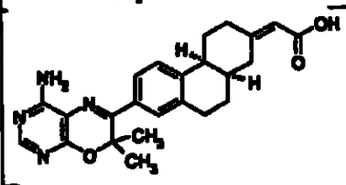
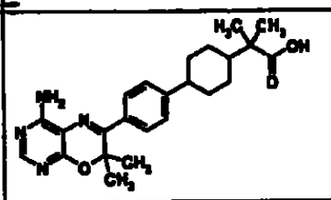
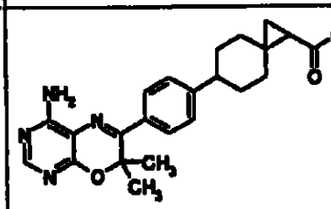
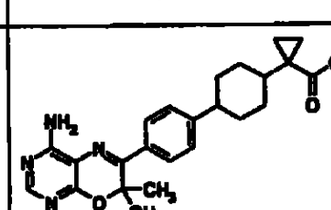
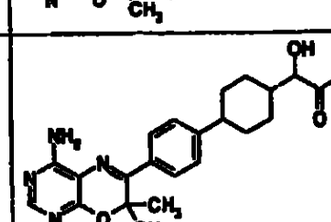
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Tabla 9

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
9			1.34 (d, J = 6.8 Hz, 3H), 1.25-1.30 (m, 2H), 1.48-1.59 (m, 2H), 1.71 (s, 6H), 1.91-2.00 (m, 4H), 2.39-2.40 (m, 1H), 2.48 (s, 3H), 2.51-2.57 (m, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H)	CDCl3
9-2				
9-3			1.10-1.30 (m, 2H), 1.48-1.80 (m, 13H), 2.17 (d, J = 6.8 Hz, 2H), 2.45-2.80 (m, 1H), 7.34 (d, J = 8 Hz, 2H), 7.38 (brs, 1H), 7.71 (d, J = 8Hz, 2H), 7.74 (brs, 1H), 12.04 (brs, 1H)	DMSO-d6

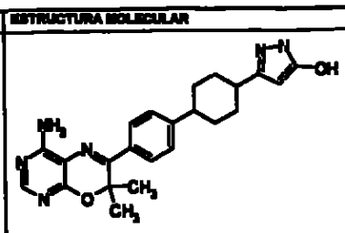
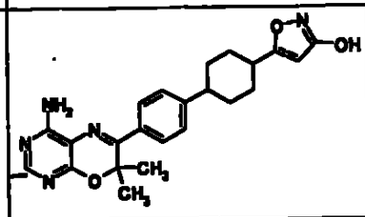
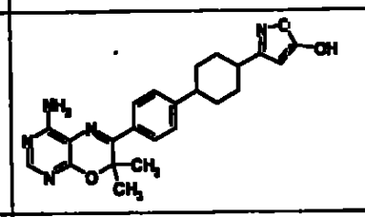
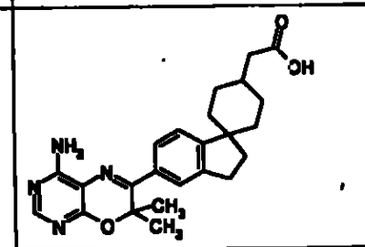
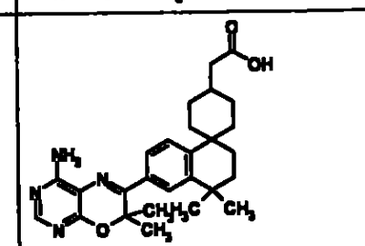
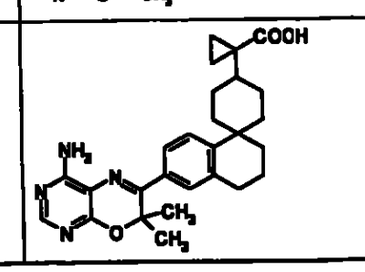
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Tabla 10

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
10			0.86 (t, J = 7.1 Hz, 3H), 1.06-2.02 (m, 19H), 6.97 (bra, 2H), 7.30 (d, J = 7.8 Hz, 2H), 7.66 (d, J= 7.8 Hz, 2H), 7.95 (s, 1H), 12.05 (s, 1H)	DMSO-d6, 400MHz
10-2			1.76-1.85 (m, 9H), 1.96-2.07 (m, 1H), 2.35-2.48 (m, 4H), 2.86-2.93 (m, 2H), 3.03-4.02 (m, 1H), 3.82 (brd, J = 12 Hz, 1H), 5.81 (s, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.36-7.40 (m, 2H), 8.17 (s, 1H)	CDCl3, 400MHz
10-3			1.08 (s, 6H), 1.14-1.22 (m, 2H), 1.40-1.48 (m, 2H), 1.61-1.75 (m, 10H), 1.82-1.85 (m, 2H), 7.3 (bra, 2H), 7.31 (d, J = 7.7 Hz, 2H), 7.64 (d, J = 7.7 Hz, 2H), 7.99 (s, 1H)	DMSO-d6, 400MHz
10-4			0.87-0.93 (m, 1H), 0.97 (t, J = 4.9 Hz, 1H), 1.02-1.10 (m, 1H), 1.20-1.31 (m, 1H), 1.46 (dd, J = 8.4 Hz, J = 2.1 Hz, 1H), 1.67-1.85 (m, 10H), 1.91-1.98 (m, 1H), 2.63-2.72 (m, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.69 (d, J = 8.3 Hz, 2H), 8.06 (s, 1H)	DMSO-d6, 400MHz
10-5.			0.75 (m, 2H), 0.99 (m, 2H), 1.38-1.62 (m, 12H), 1.69-1.87 (m, 4H), 6.97 (br s, 2H), 7.29 (d, J= 8.2Hz, 2H), 7.63 (d, J = 8.2Hz, 2H), 7.94 (s, 1H), 12.00 (s, 1H)	DMSO-d6, 400MHz
10-6			1.25-1.56 (m, 4H), 1.59 (s, 6H), 1.62-1.72 (m, 3H), 1.80-1.87 (m, 2H), 2.43-2.85 (m, 1H), 3.82 (br s, 1H), 5.05 (bra, 1H), 6.98 (bra, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 8.2 Hz, 2H), 7.94 (s, 1H), 12.03 (bra, 1H)	DMSO-d6, 400MHz

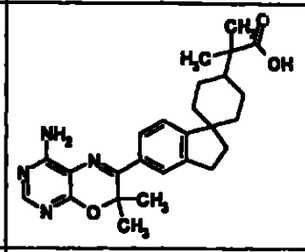
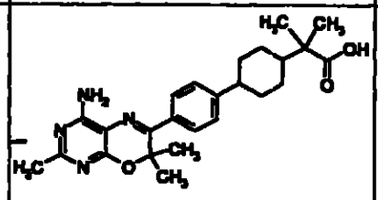
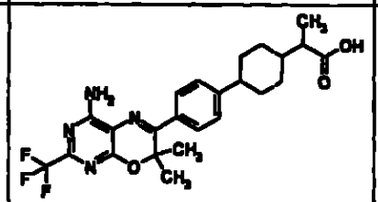
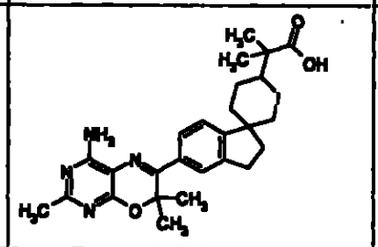
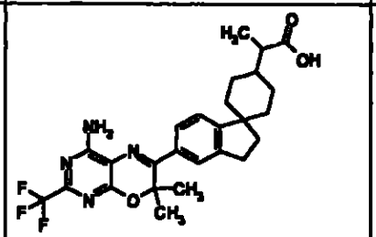
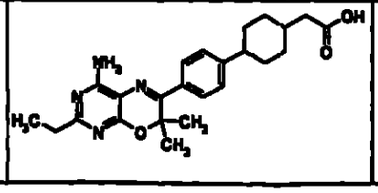
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Tabla 10 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	RMN(δ)	SOLVENTE
10-7			1.5-1.85 (m, 6H), 1.80 (s, 6H), 2.08 (m, 2H), 2.22 (m, 2H), 2.72-2.90 (m, 2H), 5.67 (s, 1H), 7.20-7.5 (m, 2H), 7.51 (d, J= 8.2 Hz, 2H), 7.84 (d, J= 8.2 Hz, 2H), 8.18 (s, 1H)	DMSO-d6, 400MHz
10-8			1.5-1.85 (m, 6H), 1.78 (s, 6H), 2.0-2.1 (m, 2H), 2.2-2.3 (m, 2H), 2.75-2.95 (m, 2H), 5.94 (s, 1H), 7.10-7.2 (m, 1H), 7.50 (d, J= 8.5 Hz, 2H), 7.83 (d, J= 8.5 Hz, 2H), 8.12 (s, 1H)	DMSO-d6, 400MHz
10-9			1.80-1.85 (m, 6H), 1.77 (s, 6H), 2.0-2.1 (m, 2H), 2.2-2.3 (m, 2H), 2.85-2.95 (m, 2H), 5.30 (s, 1H), 7.10-7.20 (m, 1H), 7.49 (d, J= 8.1 Hz, 2H), 7.81 (d, J= 8.1 Hz, 2H), 8.11 (s, 1H)	DMSO-d6, 400MHz
10-10			1.05-1.20 (m, 2H), 1.35-2.07 (m, 15H), 2.15 (d, J = 6.9Hz, 2H, major isomer only), 2.29 (d, J = 7.4 Hz, 2H, minor isomer only), 2.77-2.80 (m, 2H), 6.97 (br s, 2H), 7.03 (d, J = 7.9 Hz, 1H), 7.25-7.30 (m, 2H), 7.97 (s, 1H)	CDCl3, 400MHz
10-11			1.05-1.17 (m, 6H), 1.35-1.71 (m, 17H), 2.02 (d, J = 6.9 Hz, 2H), 6.37 (brs, 2H), 7.13-7.21 (m, 2H), 7.31 (s, 1H), 7.88 (s, 1H)	CDCl3, 400MHz
10-12			0.72-0.76 (m, 2H), 0.99 -1.03 (m, 2H), 1.40-1.82 (m, 19H), 2.75 (t, J = 6.0 Hz), 7.15 (brs, 2H), 7.36 (s, 1H), 7.46 (s, 2H), 7.99 (s, 1H)	DMSO-d6, 400MHz

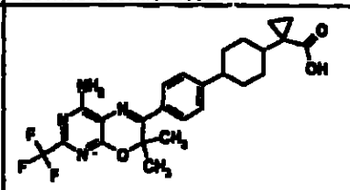
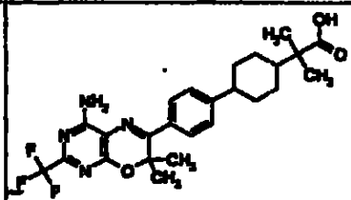
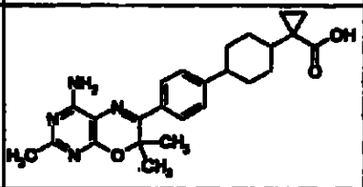
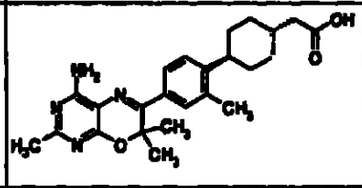
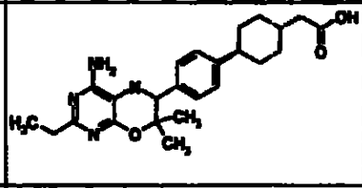
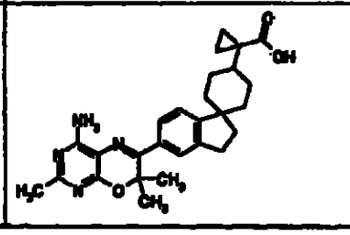
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Tabla 10 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	RMN(δ)	SOLVENTE
10-13			1.23 (s, 6H), 1.21-1.45 (m, 4H), 1.55-1.85 (m, 7H), 1.81 (s, 6H), 2.08 (m, 2H), 2.96 (m, 2H), 7.25 (m, 1H), 7.51-7.54 (m, 3H), 12.0 (bns, 1H)	DMSO-d6, 400MHz
10-14			1.06 (s, 6H), 1.15-1.28 (m, 2H), 1.42-1.51 (m, 2H), 1.60-1.66 (m, 7H), 1.68-1.73 (m, 2H), 1.82-1.86 (m, 2H), 2.34 (s, 3H), 2.50-2.63 (m, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.56 (bns, 2H), 7.86 (d, J = 8.0 Hz, 2H)	DMSO-d6, 400MHz
10-15			1.06 (d, J = 5.6 Hz, 3H), 1.13-1.24 (m, 2H), 1.42-1.53 (m, 2H), 1.54-1.60 (m, 7H), 1.71-1.82 (m, 4H), 2.16 (quin, J = 6.8 Hz, 1H), 2.51-2.58 (m, 1H), 7.32 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.8 Hz, 2H), 12.06 (bns, 1H)	DMSO-d6, 400MHz
10-16			1.23 (s, 6H), 1.20-1.50 (m, 3H), 1.55-1.85 (m, 7H), 1.80 (s, 6H), 2.08 (m, 2H), 2.65 (s, 3H), 2.96 (m, 2H), 6.80 (bs, 1H), 7.25 (m, 1H), 7.51-7.54 (m, 2H), 10.75 (bns, 1H)	CDCl3, 400MHz
10-17			1.24 (d, J = 7.0 Hz, 3H), 1.20-1.50 (m, 3H), 1.55-1.85 (m, 7H), 1.75 (s, 6H), 2.08 (m, 2H), 2.48 (m, 1H), 2.96 (m, 2H), 5.75 (bns, 1H), 7.15-7.25 (m, 3H), 7.45-7.50 (m, 1H)	CDCl3, 400MHz
10-18			1.12-1.22 (m, 5H), 1.45-1.54 (m, 2H), 1.60 (s, 6H), 1.75-1.85 (m, 8H), 2.16 (d, J = 7.2 Hz, 2H), 2.45-2.53 (m, 1H), 3.42-3.48 (m, 2H), 7.40 (bns, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 12.05 (bns, 1H)	DMSO-d6, 400MHz

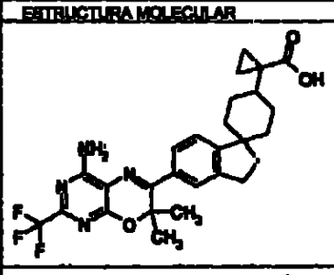
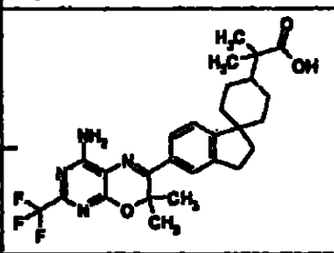
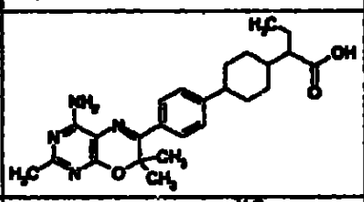
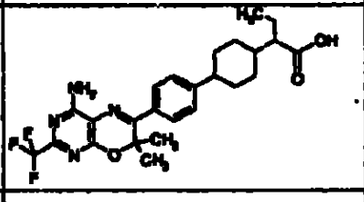
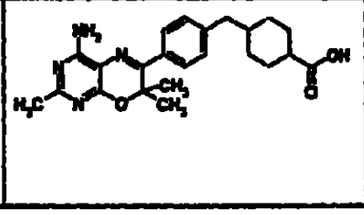
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Tabla 10 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
10-19			0.84-0.88 (m, 2H), 1.27-1.33 (m, 2H), 1.44-1.53 (m, 8H), 1.76 (s, 6H), 1.84-1.90 (m, 2H), 1.94-2.01 (m, 2H), 2.55-2.62 (m, 1H), 5.76 (bra, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H)	CDCl3, 400MHz
10-20			1.23 (s, 6H), 1.25-1.55 (m, 8H), 1.76 (s, 6H), 1.83-1.89 (m, 2H), 1.98-2.04 (m, 2H), 2.52-2.60 (m, 1H), 5.70 (bra, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H)	CDCl3, 400MHz
10-21			0.83-0.88 (m, 2H), 1.27-1.31 (m, 2H), 1.47-1.60 (m, 8H), 1.72 (s, 6H), 1.85-1.91 (m, 2H), 1.93-2.00 (m, 2H), 2.44 (s, 3H), 2.55-2.62 (m, 1H), 6.13 (bra, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H)	CDCl3, 400MHz
10-22			1.11-1.22 (m, 2H), 1.43-1.51 (m, 13H), 2.16 (d, J = 5.3 Hz, 2H), 2.34 (s, 3H), 2.35 (s, 3H), 2.62-2.74 (m, 1H), 7.29 (d, J = 8.5 Hz, 1H), 7.46-7.52 (m, 4H)	DMSO-d6, 400MHz
10-23			1.08-1.21 (m, 11H), 1.42-1.53 (m, 2H), 1.69-87 (m, 8H), 2.15 (d, J = 7.2 Hz, 2H), 2.43-2.52 (m, 3H), 4.07 (s, 1H), 5.10 (s, 1H), 6.14 (s, 2H), 7.28 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 12.08 (bra, 1H)	DMSO-d6, 400MHz
10-24			0.88 (m, 2H), 1.3 (m, 2H), 1.50-1.99 (m, 16H), 1.79 (s, 6H), 2.1 (m, 2H), 2.65 (s, 3H), 2.96 (m, 2H), 6.5 (bra, 1H), 7.18-7.25 (m, 1H), 7.45-7.80 (m, 2H), 10.5 (bra, 1H)	CDCl3, 400MHz

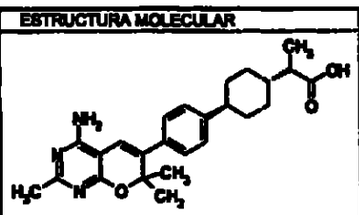
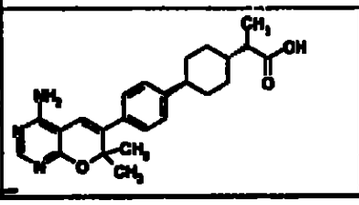
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Tabla 10 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR(δ)	SOLVENTE
10-26			0.76 (m, 2H), 1.02 (m, 2H), 1.45-1.53 (m, 10H),1.7 (s, 6H), 2.0 (m, 2H), 2.95 (m, 2H), 3.33 (m, 1H), 7.15-7.25 (m, 1H), 7.45-7.50 (m, 2H), 12.0 (bra, 1H)	CDCl3, 400MHz
10-28			1.0 (m, 2H), 1.23 (s, 6H), 1.25-1.50 (m, 3H), 1.55-1.85 (m, 6H), 1.75 (s, 6H), 2.05 (m, 2H), 2.95 (m, 2H), 5.91 (bra, 1H), 7.15-7.25 (m, 2H), 7.45-7.50 (m, 1H)	CDCl3, 400MHz
10-27			0.86 (t, J = 7.2 Hz, 3H), 1.05-1.12 (m, 2H), 1.33-1.50 (m, 10H), 1.70-2.04 (m, 6H), 2.25 (s, 3H), 2.45-2.62 (m, 1H), 6.80 (bra, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H)	DMSO-d6, 400MHz
10-25			0.99 (t, J = 7.2 Hz, 3H), 1.25-1.25 (m, 18H), 2.50-2.60 (m, 1H), 5.75 (bra, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H)	CDCl3, 400MHz
10-29			0.90-1.05 (m,1H), 1.10-1.25 (m, 2H), 1.40-1.50 (m, 2H), 1.57 (s, 6H), 1.60-1.70 (m, 2H), 1.80-1.90 (m, 2H), 1.90 (s, 2H), 2.24 (s, 3H), 2.35-2.50 (m, 1H), 6.81 (bra, 2H), 7.21 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 8.2 Hz, 2H), 11.9 (bra, 1H)	DMSO-d6, 400MHz

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Tabla 10 (Continuación)

NUEVO EJEMPLO #	ESTRUCTURA MOLECULAR	P.F.	NMR (δ)	SOLVENTE
10-30			1.05 (d, J = 6.9 Hz, 3H), 1.10-1.25 (m, 2H), 1.41-1.51 (m, 2H), 1.82-2.01 (m, 7H), 1.71-1.87 (m, 4H), 2.16-2.22 (m, 1H), 2.39 (s, 3H), 2.44-2.50 (m, 1H), 6.66 (s, 1H), 7.30 (Abq, J = 8.0 Hz 2H), 8.0 (bra, 2H)	DMSO-d6, 400MHz
10-31			1.05 (d, J = 6.9 Hz, 3H), 1.10-1.25 (m, 2H), 1.41-1.52 (m, 6H), 1.71-1.88 (m, 4H), 2.14-2.21 (m, 1H), 2.42-2.50 (m, 1H), 6.66 (s, 1H), 7.03 (bra, 2H), 7.27 (Abq, J = 7.9 Hz 2H), 12.0 (bra, 1H)	DMSO-d6, 400MHz

Ejemplo 10

Este ejemplo describe ensayos que pueden usarse para identificar compuestos que tienen actividad DGAT.

Pueden usarse numerosos sistemas de ensayo *in vitro* para determinar la modulación de la actividad DGAT. Ejemplos de dichos sistemas de ensayo utilizan sistemas de sobre expresión de células de insectos, preparaciones de microsoma de tejidos y cultivos celulares. En los sistemas de ensayo de preparación de microsoma de tejido y de sobre expresión de células de insectos, el sistema mismo proporciona la fuente enzimática para las mediciones de actividad. Dichas mediciones son conducidas generalmente usando substrato radiomarcado, en donde el producto radiomarcado que es generado es subsecuentemente resuelto por cromatografía en capa fina (TLC) (ver, por ejemplo, Cases y colaboradores, Proc. Natl. Acad. Sci. (1998) 95: 13018 y Cases, y colaboradores, J. Biol. Chem. (2001) 276:38870).

A título de comparación, los sistemas de ensayo basados en cultivos celulares miden la síntesis intracelular de triglicéridos por incubación de células vivientes con ácidos grasos radiomarcados. El ácido graso radiomarcado es utilizado en la biosíntesis de triglicéridos. Los triglicéridos pueden entonces ser extraídos a partir de células que usan solvente orgánico y

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se resuelven por cromatografía de capa fina para determinar el nivel de incorporación de la radiomarca como una medida de la actividad enzimática (ver por ejemplo, Cases, y colaboradores, J. Biol. Chem. (2001) 276:38870).

Ensayos Basados en Células

En un ensayo celular preferido células CaCO2 de tumor de colon humano, HepG2 de hepatoma humano, o 3T3-L1 de adipocito de ratón (diferenciadas o no diferenciadas como se describe posteriormente) son cultivadas a confluencia en placas de 24 pocillos. El medio es reemplazado con medio libre de suero y las células son incubadas por 24-48 horas adicionales. Después, el medio es reemplazado con medio libre de suero que contiene 400 µM de ácido oleico (complejado con BSA, 2:1 mol:mol) y el compuesto a dosis variables en un volumen final de 200 µl por pocillo. Las células son incubadas por 30 minutos antes de añadir 0.1 μC_i de ácido oleico marcado con ^{14}C directamente a las células y se continúa la incubación por 10-10 minutos dependiendo del tipo de células. Las células son lavadas dos veces con 1 ml de PBS y es secada con aire a 37 °C por 10 minutos. Se extraen los lípidos celulares con 0.5 ml de hexano:alcohol isopropílico (3;2 v/v) por 5 minutos dos veces. Se evaporan a sequedad los extractos lipídicos y se usan para TLC usando hexano-éter etílico:ácido acético (80:20:1) v/v) como solvente. Las bandas radioactivas son

visualizadas y cuantificadas por exposición a película de rayos-X o a la pantalla fósforo-formadora de imágenes.

La diferenciación de células 3T3-L1 en adipocitos es inducida por incubación de células confluentes en medio que contiene suero al 10 %, insulina (10 µg/ml), dexametasona (1 µM), isobutilmetil xantina (IBMX, 0.5 mM), y tri-iodotironina (T3, 10 nM). Después de 2 días, las células se mantienen en suero, insulina, T3, y BRL49653 (1 µM) que contiene medio para 4 - 10 días.

Ensayos Bioquímicos

Un ensayo preferido que puede usarse para identificar inhibidores de DGAT involucra un Ensayo de Proximidad por Centelleo para cribado de alto rendimiento (SPA). En un ensayo tal DGAT1 humano es clonado a partir de una biblioteca de cDNA de hígado humano. Se usa la PCR para añadir un sitio de restricción y epítope indicador en la mayoría de los extremos 5' y un sitio de restricción en el extremo 3' de la secuencia. Después de lo cual puede generarse el baculovirus de DGAT1 con marca indicadora (FT) humano usando un Sistema de Expresión de Baculovirus Bac-to-Bac® (Invitrogen). Las células de insectos (por ejemplo, sf9, sf21, o "High Five") son infectadas por 24 a 72 horas y colectadas por centrifugación. Los compactados celulares son resuspendidos en regulador de homogeneización y son lisados usando un dispositivo de

homogeneización, tal como un Microfluidizer. Se colectan las membranas celulares totales por ultracentrifugación a 45,000 rpm por 1 hora.

Una pequeña alícuota (0.2 µg/pocillo) de membrana es incubada con 10 µM de compuesto o cloruro mercúrico (como control positivo para inhibición) en la presencia de substrato enzimático, dioleoil glicerol (200 µM) en placas de 384 pocillos, volumen final de 50 µl por pocillo. La reacción es iniciada por adición de substrato radioactivo, coenzima A marcada con acil ^{14}C (25 µM, tal como decanoil CoA, palmitoil CoA, oleoil CoA), y se incuba a temperatura ambiente por 2 horas. La reacción es detenida por adición de perlas de SPA con Aglutinina de Germen de Trigo (WGA) (0.2 mg) en cloruro mercúrico. Las membranas celulares se dejan acoplar a las perlas toda la noche. La señal puede medirse usando, por ejemplo, un Lector de Placa para Imagen por Quimioluminiscencia (CLIPR, Chemiluminiscence Image Plate Reader) o dispositivo de TopCount.

Se encontró que los compuestos de la presente invención evaluados por medio de los ensayos descritos anteriormente, tuvieron actividad inhibidora de DGAT. Ver la Tabla 11 siguiente.

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Tabla 11

Ejemplo	hDGAT1 IC_{50}*	Ejemplo	hDGAT1 IC_{50}*	Ejemplo	hDGAT1 IC_{50}*
1	+	2-6	++	2-48	++
1-2	+	2-7	++	2-49	++
1-3	+	2-8	+	2-50	++
1-4	+	2-9	+	2-51	++
1-5	+	2-10	+	2-52	++
1-6	+	2-11	+	2-53	++
1-7	+	2-12	+	2-54	++
1-8	+	2-13	+	2-55	++
1-9 —	+	2-14	+	2-56	++
1-10	+	2-15	+	2-59	++
1-11	+	2-16	+	2-60	++
1-12	+	2-17	+	2-61	++
1-13	+	2-18	++	2-62	++
1-14	+	2-19	+	2-63	++
1-15	+	2-20	+	2-64	++
1-16	+	2-21	+	2-65	+++
1-17	+	2-22	+	2-66	+
1-18	+	2-23	+	2-67	++
1-19	+	2-24	+	2-68	+
1-20	+	2-25	+	2-69	+++
1-21	+	2-26	++	2-70	++
1-22	+	2-27	+	2-71	+
1-23	+	2-28	+	2-72	++
1-24	+	2-29	+	2-73	++
1-25	+	2-30	+	2-74	+++
1-26	+	2-31	+	2-75	+
1-27	+	2-32	+	2-76	++
1-28	+	2-33	++	2-77	++
1-29	+	2-34	++	2-78	++
1-30	+	2-35	+	2-79	++
1-31	+	2-36	++	2-80	++
1-32	+	2-37	+	2-81	+
1-33	+	2-38	+	2-82	+
1-34	+	2-39	+	2-83	+
1-35	+	2-40	+++	2-84	+
1-36	+	2-41	+	2-85	+
1-37	+	2-42	++	2-86	+
2	+++	2-43	++	2-87	+
2-2	++	2-44	++	2-88	+
2-3	++	2-45	++	2-89	+
2-4	+++	2-46	++	2-90	+
2-5	++	2-47	++	2-91	++

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Tabla 11 (Continuación)

Ejemplo	hDGATI IC_{50}*	Ejemplo	hDGATI IC_{50}*	Ejemplo	hDGATI IC_{50}*
2-92	++	2-138	++	2-184	++
2-93	++	2-139	++	2-185	++
2-94	++	2-140	++	2-186	++
2-95	++	2-141	++	2-187	+++
2-96	++	2-142	++	2-188	++
2-97	++	2-143	+++	2-189	++
2-98	++	2-144	++	2-190	++
2-99	++	2-145	++	2-191	+++
2-100	++	2-146	++	2-192	+++
2-101	++	2-147	++	2-193	++
2-102	++	2-148	+++	2-194	++
2-103	++	2-149	++	2-195	++
2-104 --	++	2-150	++	2-196	++
2-105	++	2-151	+++	2-197	++
2-106	++	2-152	++	2-198	++
2-107	+++	2-153	+++	2-200	+++
2-108	++	2-154	++	2-201	+++
2-109	++	2-155	++	2-202	++
2-110	++	2-156	++	2-203	++
2-111	++	2-157	+++	2-204	++
2-112	++	2-158	++	2-205	++
2-113	++	2-159	++	2-206	++
2-114	++	2-160	++	2-207	++
2-115	+	2-161	++	2-208	++
2-116	++	2-162	++	2-209	++
2-117	++	2-163	++	2-210	++
2-118	++	2-164	++	2-211	++
2-119	++	2-165	++	2-212	+++
2-120	++	2-166	++	2-213	++
2-121	++	2-167	++	2-214	+++
2-122	++	2-168	++	2-215	++
2-123	++	2-169	++	2-216	++
2-124	++	2-170	++	2-217	++
2-125	+++	2-171	+	2-218	++
2-126	++	2-172	++	2-219	++
2-127	++	2-173	++	2-220	++
2-128	++	2-174	++	2-221	+
2-129	++	2-175	++	2-222	+
2-130	++	2-176	++	2-223	+
2-131	++	2-177	++	2-224	+
2-132	++	2-178	++	2-225	+
2-133	++	2-179	++	2-226	+
2-134	+++	2-180	++	2-227	+
2-135	++	2-181	++	2-228	+
2-136	++	2-182	++	2-229	+
2-137	+++	2-183	++	2-230	++

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Tabla 11 (Continuación)

Ejemplo	hDGAT1 IC_{50}*
2-232	++
2-233	+
2-234	++
2-235	++
2-236	++
2-237	++
2-238	+
2-239	+
2-240	++
2-241	++
2-242	+
2-243	++
2-244	++
2-245	++
2-246	++
2-247	++
2-248	++
2-249	++
2-250	++
2-251	++
2-252	++
2-253	+++
2-254	++
2-255	++
2-256	++
2-257	++
2-258	++
2-259	++
2-260	++
2-261	++
2-262	++
2-263	+++
2-264	++
3	++
3-2	+
3-3	+
4	+
4-2	+
4-3	+

Ejemplo	hDGAT1 IC_{50}*
4-4	++
4-5	+
4-6	+
4-7	+
5	+
5-2	+
5-3	+
6	+++
6-2	++
6-3	++
6-4	+
6-5	++
6-9	+++
6-10	++
6-11	++
6-12	+++
6-13	+++
6-14	++
6-15	++
6-16	+
6-17	+
6-18	++
6-19	++
6-20	+++
6-21	++
6-22	++
6-23	++
6-24	++
6-25	++
7	++
7-2	++
7-3	+
7-4	++
7-5	++
8	+++
8-2	++
8-3	++
8-4	++
8-5	++

Ejemplo	hDGAT1 IC_{50}*
8-6	++
8-7	+++
9	++
9-2	++
9-3	+++
10	+++
10-2	++
10-3	+++
10-4	++
10-5	++
10-6	++
10-7	++
10-8	++
10-9	++
10-10	+++
10-11	++
10-12	++
10-13	+++
10-14	++
10-15	+++
10-16	++
10-17	+++
10-18	++
10-19	++
10-20	++
10-21	++
10-22	++
10-23	++
10-24	++
10-25	++
10-26	++
10-27	++
10-28	+++
10-29	++
10-30	++
10-31	++

* Leyenda:

"+" representa: valor de IC_{50} > 0.1 µM

"++" representa: 0.1 µM ≥ valor de IC_{50} ≥ 0.01 µM

"+++" representa : valor de IC_{50} < 0.01 µM

Todas las publicaciones y solicitudes de patentes citadas en esta especificación se incorporan a la presente como referencia como si cada publicación o solicitud de patente individual fuera específica e individualmente indicada para ser incorporada como referencia. Aunque la invención precedente ha sido descrita con algún detalle a manera de ilustración y ejemplo para propósitos de claridad de comprensión, será fácilmente obvio para los expertos en la materia a la vista de lo expuesto en esta invención que pueden hacerse a la misma ciertos cambios y modificaciones sin alejarse del espíritu o el alcance de las reivindicaciones anexas.

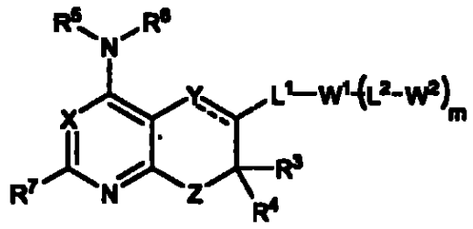
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NOVEDAD DE LA INVENCION

Habiendo descrito la presente invención, se considera como novedad, y por lo tanto se reclama como propiedad lo contenido en las siguientes:

REIVINDICACIONES

1. Un compuesto de Fórmula (I):



I

o una sal, profármaco o estereoisómero del mismo, aceptables farmacéuticamente, caracterizado porque

X es seleccionado del grupo que consiste de $C(R^1)$ y N;

Y es seleccionado del grupo que consiste de $C(R^1)$, $C(R^2)(R^2)$, N y $N(R^2)$;

Z es seleccionado del grupo que consiste de O o S;

W^1 es un elemento substituido o no substituido seleccionado del grupo que consiste de ciclo(C_3-C_8)-alquilo, heterociclo-(C_3-C_8)-alquilo, arilo y heteroarilo;

W^2 es un elemento substituido o no substituido

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seleccionado del grupo que consiste de ciclo-(C_3-C_8)-alquilo, heterociclo-(C_3-C_8)-alquilo, arilo y heteroarilo

L^1, es seleccionado del grupo que consiste de un enlace, (C_1-C_4)-alquileno, (C_2-C_4)-alquenileno, O y $N(R^a)C(O)$;

L^2, es seleccionado del grupo que consiste de un enlace, O, (C_1-C_4)-alquileno, (C_2-C_4)-alquenileno, (C_1-C_4)-heteroalquileno y $N(R^a)C(O)$;

el subíndice m es 0 o 1;

opcionalmente cuando m es 1 y L^2 es un enlace, un substituyente sobre W^2 puede ser combinado con un substituyente sobre W^1 para formar un anillo de 5-, 6- o 7- elementos fusionado a W^1 y espiro o fusionado a W^2, en donde el anillo es saturado o insaturado y tiene 0, 1 o 2 heteroátomos seleccionados del grupo que consiste de N, O y S como elementos del anillo;

cada R^1 es seleccionado independientemente del grupo que consiste de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, fluoro-(C_1-C_8)-alquilo, arilo, aril-(C_1-C_4)-alquilo, $C(O)R^a$, CO_2R^a y $C(O)NR^aR^b$;

cada R^2 es independientemente seleccionado del grupo que consiste de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, fluoro-(C_1-C_8)-alquilo, $C(O)R^a$, CO_2R^a, $C(O)NR^aR^b$, arilo y aril-(C_1-C_4)-alquilo;

R^3 y R^4 son seleccionados independientemente del grupo

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que consiste de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, $C(O)R^a$, CO_2R^a, $C(O)NR^aR^b$ y (C_1-C_4)-alquileno-OR^a;

opcionalmente, R^3 y R^4 pueden combinarse para formar un anillo espiro de 3-, 4-, 5- o 6- elementos;

opcionalmente R^2, R^3 o R^4 pueden combinarse con W^1 para formar un anillo fusionado de 5-, 6- o 7- elementos que tiene de 0 a 3 heteroátomos seleccionados del grupo que consiste de N, O y S;

R^5 y R^6 son seleccionados independientemente del grupo que consiste de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)alquinilo, $C(O)R^a$ y CO_2R^a;

opcionalmente, R^5 y R^6 pueden combinarse con el átomo de nitrógeno para formar un anillo de 5-, 6- o 7- elementos;

opcionalmente, cuando X es $C(R^1)$ o cuando Y incluye un grupo R^1 o R^2, R^5 o R^6 puede combinarse con R^1 o R^2 para formar un anillo fusionado de 5-, 6- o 7- elementos que contiene el átomo de nitrógeno al cual está fijado R^5 o R^6;

R^7 es seleccionado del grupo que consiste de H, (C_1-C_8)-alquilo, halo-(C_1-C_4)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, $C(O)R^a$, OR^a y NR^aR^b;

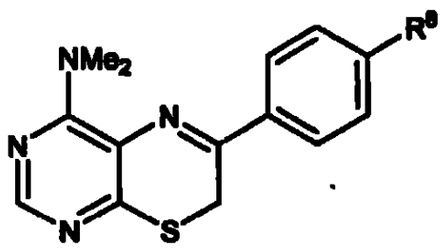
opcionalmente, cuando X es $C(R^1)$, R^7 puede combinarse con R^1 para formar un anillo fusionado de 5-, 6- o 7- elementos;

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cada R^a y R^b es seleccionado independientemente de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, fluoro-(C_1-C_8)-alquilo, arilo, aril-(C_1-C_4)-alquilo; y

la línea punteada indica un enlace opcional;

con la condición de que el compuesto sea diferente de



en donde R^8 es seleccionado del grupo que consiste de H, NO_2, Cl, metoxi, metilo o fenilo.

2. Un compuesto de conformidad con la reivindicación 1, caracterizado porque X es N.

3. Un compuesto de conformidad con la reivindicación 2, caracterizado porque Z es O.

4. Un compuesto de conformidad con la reivindicación 1, caracterizado porque L^1 es un enlace y W^1 es un elemento substituido o no substituido seleccionado de benceno, piridina, tiofeno, oxazol, tiazol, benzoxazol, benzotiazol, benzofurano, benzotiofeno, (C_4-C_7)-cicloalcano, (C_5-C_7)-cicloalqueno, 1, 2, 3, 4-tetrahidronaftaleno e indano.

5. Un compuesto de conformidad con la reivindicación 4, caracterizado porque W^1 es un elemento substituido o no

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substituido seleccionado de benceno, piridina, tiofeno, 1, 2, 3, 4-tetrahidronaftaleno e indano.

6. Un compuesto de conformidad con la reivindicación 5, caracterizado porque el subíndice m es 1.

7. Un compuesto de conformidad con la reivindicación 5, caracterizado porque el subíndice m es 1 y L^2 es un enlace.

8. Un compuesto de conformidad con la reivindicación 7, caracterizado porque W^2 es un elemento substituido o no substituido seleccionado del grupo que consiste de benceno, piridina, (C_4-C_7)-cicloalcano, (C_5-C_7)-cicloalqueno, pirrolidina, piperidina, piperazina y morfolina.

9. Un compuesto de conformidad con la reivindicación 4, caracterizado porque R^5 y R^6 son seleccionados independientemente del grupo que consiste de H, (C_1-C_6)-alquilo, $C(O)R^a$ y CO_2R^a.

10. Un compuesto de conformidad con la reivindicación 9, caracterizado porque R^5 y R^6 son seleccionados independientemente del grupo que consiste de H y (C_1-C_8)-alquilo.

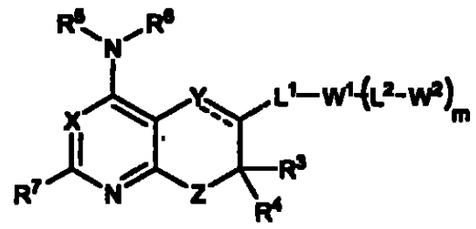
11. Un compuesto de conformidad con la reivindicación 10, caracterizado porque R^3 y R^4 son seleccionados independientemente del grupo que consiste de H y (C_1-C_8)-alquilo.

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12. Un compuesto de conformidad con la reivindicación 11, caracterizado porque R^7 es seleccionado del grupo que consiste de H, (C_1-C_8)-alquilo, halo-(C_1-C_4)-alquilo, OH y NR^aR^b en donde R^a y R^b son seleccionados independientemente del grupo que consiste de H y (C_1-C_8)-alquilo.

13. Un compuesto de conformidad con la reivindicación 11, caracterizado porque R^7 es H, (C_1-C_8)-alquilo o halo-(C_1-C_4)-alquilo.

14. Una composición farmacéutica caracterizada porque comprende un excipiente aceptable farmacéuticamente y un compuesto de Fórmula (I):



I

o una sal, profármaco o estereoisómero del mismo, aceptables farmacéuticamente, caracterizado porque

X es seleccionado del grupo que consiste de $C(R^1)$ y N;

Y es seleccionado del grupo que consiste de $C(R^1)$, $C(R^2)(R^2)$, N y $N(R^2)$;

Z es seleccionado del grupo que consiste de O y S;

W^1 es un elemento substituido o no substituido

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seleccionado del grupo que consiste de ciclo(C_3-C_8)-alquilo, heterociclo-(C_3-C_8)-alquilo, arilo y heteroarilo;

W^2 es un elemento substituido o no substituido seleccionado del grupo que consiste de ciclo-(C_3-C_8)-alquilo, heterociclo-(C_3-C_8)-alquilo, arilo y heteroarilo

L^1, es seleccionado del grupo que consiste de un enlace, (C_1-C_4)-alquileno, (C_2-C_4)-alquenileno, O y $N(R^a)C(O)$;

L^2, es seleccionado del grupo que consiste de un enlace, O, (C_1-C_4)-alquileno, (C_2-C_4)-alquenileno, (C_1-C_4)-heteroalquileno y $N(R^a)C(O)$;

el subíndice m es 0 o 1;

opcionalmente cuando m es 1 y L^2 es un enlace, un substituyente sobre W^2 puede ser combinado con un substituyente sobre W^1 para formar un anillo de 5-, 6- o 7- elementos fusionado a W^1 y espiro o fusionado a W^2, en donde el anillo es saturado o insaturado y tiene 0, 1 o 2 heteroátomos seleccionados del grupo que consiste de N, O y S como elementos del anillo;

cada R^1 es seleccionado independientemente del grupo que consiste de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, fluoro-(C_1-C_8)-alquilo, arilo, aril-(C_1-C_4)-alquilo, $C(O)R^a$, CO_2R^a y $C(O)NR^aR^b$;

cada R^2 es independientemente seleccionado del grupo que consiste de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-

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C_8)-alquinilo, fluoro-(C_1-C_8)-alquilo, $C(O)R^a$, CO_2R^a, $C(O)NR^aR^b$,. arilo y aril-(C_1-C_4)-alquilo;

R^3 y R^4 son seleccionados independientemente del grupo que consiste de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, $C(O)R^a$, CO_2R^a, $C(O)NR^aR^b$ y (C_1-C_4)-alquileno-OR^a;

opcionalmente, R^3 y R^4 pueden combinarse para formar un anillo espiro de 3-, 4-, 5- o 6- elementos;

opcionalmente R^2, R^3 o R^4 pueden combinarse con W^1 para formar un anillo fusionado de 5-, 6- o 7- elementos que tiene de 0 a 3 heteroátomos seleccionados del grupo que consiste de N, O y S;

R^5 y R^6 son seleccionados independientemente del grupo que consiste de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, $C(O)R^a$ y CO_2R^a;

opcionalmente, R^5 y R^6 pueden combinarse con el átomo de nitrógeno para formar un anillo de 5-, 6- o 7- elementos;

opcionalmente, cuando X es $C(R^1)$ o cuando Y incluye un grupo R^1 o R^2, R^5 o R^6 puede combinarse con R^1 o R^2 para formar un anillo fusionado de 5-, 6- o 7- elementos que contiene el átomo de nitrógeno al cual está fijado R^5 o R^6;

R^7 es seleccionado del grupo que consiste de H, (C_1-C_8)-alquilo, halo-(C_1-C_4)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, $C(O)R^a$, OR^a y NR^aR^b;

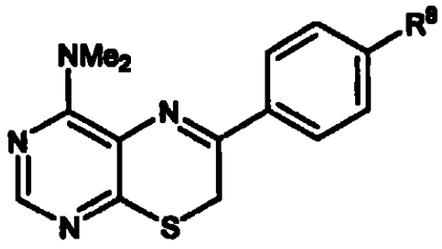
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opcionalmente, cuando X es $C(R^1)$, R^7 puede combinarse con R^1 para formar un anillo fusionado de 5-, 6- o 7-elementos;

cada R^a y R^b es seleccionado independientemente de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, fluoro-(C_1-C_8)-alquilo, arilo, aril-(C_1-C_4)-alquilo; y

la línea punteada indica un enlace opcional;

con la condición de que el compuesto sea diferente de



en donde R^8 es seleccionado del grupo que consiste de H, NO_2, Cl, metoxi, metilo o fenilo.

15. Una composición farmacéutica de conformidad con la reivindicación 14, caracterizada porque X es N.

16. Una composición farmacéutica de conformidad con la reivindicación 15, caracterizada porque Z es O.

17. Una composición farmacéutica de conformidad con la reivindicación 16, caracterizado porque L^1 es un enlace y W^1 es un elemento substituido o no substituido seleccionado del grupo que consiste de benceno, piridina, tiofeno, oxazol, tiazol, benzoxazol, benzotiazol, benzofurano, benzotiofeno, (C_4-C_7)-cicloalcano, (C_5-C_7)-

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cicloalqueno, 1, 2, 3, 4-tetrahidronaftaleno e indano.

18. Una composición farmacéutica de conformidad con la reivindicación 17, caracterizada porque W^1 es un elemento substituido o no substituido seleccionado del grupo que consiste de benceno, piridina, tiofeno, 1, 2, 3, 4-tetrahidronaftaleno e indano.

19. Una composición farmacéutica de conformidad con la reivindicación 18, caracterizada porque el subíndice m es 1.

20. Una composición farmacéutica de conformidad con la reivindicación 18, caracterizada porque el subíndice m es 1 y L^2 es un enlace.

21. Una composición farmacéutica de conformidad con la reivindicación 20, caracterizado porque W^2 es un elemento substituido o no substituido seleccionado del grupo que consiste de benceno, piridina, (C_4-C_7)-cicloalcano, (C_5-C_7)-cicloalqueno, pirrolidina, piperidina, piperazina y morfolina.

22. Una composición farmacéutica de conformidad con la reivindicación 17, caracterizada porque R_5 y R_6 son seleccionados independientemente del grupo que consiste de H, (C_1-C_8)-alquilo, $C(O)R^a$ y CO_2R^a.

23. Una composición farmacéutica de conformidad con la reivindicación 22, caracterizada porque R^5 y R^6 son seleccionados independientemente del grupo que consiste de

H y (C_1-C_8)-alquilo.

24. Una composición farmacéutica de conformidad con la reivindicación 23, caracterizada porque R^3 y R^4 son seleccionados independientemente del grupo que consiste de H y (C_1-C_8)-alquilo.

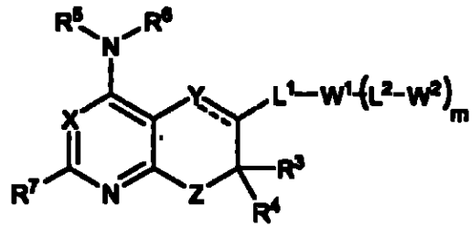
25. Una composición farmacéutica de conformidad con la reivindicación 24, caracterizada porque R^7 es seleccionado del grupo que consiste de H, (C_1-C_8)-alquilo, halo-(C_1-C_4)-alquilo, OH y NR^aR^b en donde R^a y R^b son seleccionados independientemente del grupo que consiste de H y (C_1-C_8)-alquilo.

26. Una composición farmacéutica de conformidad con la reivindicación 24, caracterizada porque R^7 es H, (C_1-C_8)-alquilo o halo-(C_1-C_4)-alquilo.

27. Un método de tratar una enfermedad o condición seleccionada del grupo que consiste de obesidad, diabetes, anorexia nerviosa, bulimia, caquexia, síndrome X, resistencia a la insulina, hiperglicemia, hiperuricemia, hiperinsulinemia, hipercolesterolemia, hiperlipidemia, dislipidemia, dislipidemia mezclada, hipertrigliceridemia, enfermedad hepática grasa no alcohólica, arterioesclerosis, falla cardíaca aguda, falla cardíaca congestiva, enfermedad de la arteria coronaria, cardiomiopatía, infarto al miocardio, angina pectoris, hipertensión, hipotensión, apoplejía, isquemia, daño por

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reperfusión isquémica, aneurisma, restenosis, estenosis vascular, tumores sólidos, cáncer de la piel, melanoma, linfoma, cáncer de seno, cáncer de pulmón, cáncer colonrectal, cáncer del estómago, cáncer del esófago, cáncer pancreático, cáncer de próstata, cáncer de riñón, cáncer de hígado, cáncer de vejiga, cáncer cervical, cáncer uterino, cáncer testicular y cáncer ovárico, caracterizado porque comprende administrar a un sujeto en necesidad del mismo una cantidad efectiva de un compuesto de Fórmula (I):



I

o una sal, profármaco o estereoisómero del mismo, aceptable farmacéuticamente, caracterizado porque

X es seleccionado del grupo que consiste de $C(R^1)$ y N;

Y es seleccionado del grupo que consiste de $C(R^1)$, $C(R^2)(R^2)$, N y $N(R^2)$;

Z es seleccionado del grupo que consiste de O o S;

W^1 es un elemento substituido o no substituido seleccionado del grupo que consiste de ciclo(C_3-C_8)-

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alquilo, heterociclo-(C_3-C_8)-alquilo, arilo y heteroarilo;

W^2 es un elemento substituido o no substituido seleccionado del grupo que consiste de ciclo-(C_3-C_8)-alquilo, heterociclo-(C_3-C_8)-alquilo, arilo y heteroarilo

L^1, es seleccionado del grupo que consiste de un enlace, (C_1-C_4)-alquileno, (C_2-C_4)-alquenileno, O y $N(R^a)C(O)$;

L^2, es seleccionado del grupo que consiste de un enlace, O, (C_1-C_4)-alquileno, (C_2-C_4)-alquenileno, (C_1-C_4)-heteroalquileno y $N(R^a)C(O)$;

el subíndice m es 0 o 1;

opcionalmente, cuandc m es 1 y L^2 es un enlace, un substituyente sobre W^2 puede ser combinado con un substituyente sobre W^1 para formar un anillo de 5-, 6- o 7- elementos fusionado a W^1 y espiro o fusionado a W^2, en donde el anillo es saturado o insaturado y tiene 0, 1 o 2 heteroátomos seleccionados del grupo que consiste de N, O y S como elementos del anillo;

cada R^1 es seleccionado independientemente del grupo que consiste de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, fluoro-(C_1-C_8)-alquilo, arilo, aril-(C_1-C_4)-alquilo, $C(O)R^a$, CO_2R^a y $C(O)NR^aR^b$;

cada R^2 es independientemente seleccionado del grupo que consiste de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, fluoro-(C_1-C_8)-alquilo, $C(O)R^a$, CO_2R^a,

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$C(O)NR^aR^b$, arilo y aril-(C_1-C_4)-alquilo;

R^3 y R^4 son seleccionados independientemente del grupo que consiste de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, $C(O)R^a$, CO_2R^a, $C(O)NR^aR^b$ y (C_1-C_4)-alquileno-OR^a;

opcionalmente, R^3 y R^4 pueden combinarse para formar un anillo espiro de 3-, 4-, 5- o 6- elementos;

opcionalmente R^2, R^3 o R^4 pueden combinarse con W^1 para formar un anillo fusionado de 5-, 6- o 7- elementos que tiene de 0 a 3 heteroátomos seleccionados del grupo que consiste de N, O y S;

R^5 y R^6 son seleccionados independientemente del grupo que consiste de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)alquinilo, $C(O)R^a$ y CO_2R^a;

opcionalmente, R^5 y R^6 pueden combinarse con el átomo de nitrógeno para formar un anillo de 5-, 6- o 7- elementos;

opcionalmente, cuando X es $C(R^1)$ o cuando Y incluye un grupo R^1 o R^2, R^5 o R^6 puede combinarse con R^1 o R^2 para formar un anillo fusionado de 5-, 6- o 7- elementos que contiene el átomo de nitrógeno al cual está fijado R^5 o R^6;

R^7 es seleccionado del grupo que consiste de H, (C_1-C_8)-alquilo, halo-(C_1-C_4)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, $C(O)R^a$, OR^a y NR^aR^b;

opcionalmente, cuando X es $C(R^1)$, R^7 puede combinarse

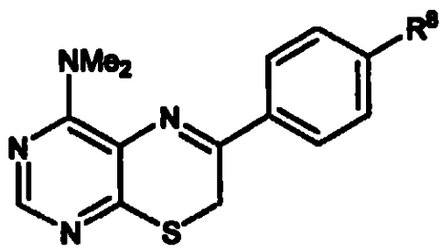
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con R^1 para formar un anillo fusionado de 5-, 6- o 7-elementos;

cada R^a y R^b es seleccionado independientemente de H, (C_1-C_8)-alquilo, (C_2-C_8)-alquenilo, (C_2-C_8)-alquinilo, fluoro-(C_1-C_8)-alquilo, arilo, aril-(C_1-C_4)-alquilo; y

la línea punteada indica un enlace opcional;

con la condición de que el compuesto sea diferente de



en donde R^8 es seleccionado del grupo que consiste de H, NO_2, Cl, metoxi, metilo o fenilo.

28. Un método de conformidad con la reivindicación 27, caracterizado porque el compuesto es administrado oralmente.

29. Un método de ccnformidad con la reivindicación 27, caracterizado porque el compuesto es administrado en combinación con un agente activo adicional.

30. Un método de conformidad con la reivindicación 29, caracterizado porque el agente activo adicional es seleccionado del grupo que consiste de un agente antihiperlipidémico; un agente elevador del HDL plasmático, un agente anti-hipercolesterolémico, un

inhibidor de HMG-CoA reductasa, un inhibidor de HMG-CoA sintasa, un inhibidor de la lipasa pancreática, SNRI, agente supresor del apetito, un modulador de PPAR, un inhibidor de MTP, un inhibidor de CETP, un inhibidor del escualeno peroxidasa, un inhibidor del escualeno sintetasa, un inhibidor de acil-co-enzima A colesterol aciltransferasa, vitamina B_3, un inhibidor de la absorción de colesterol, una resina de intercambio aniónico secuestrante de ácidos biliares, un inductor del receptor de la lipoproteína de baja densidad, un fibrato, probucol, Vitamina B_6, vitamina B_{12}, una vitamina antioxidante, un bloqueador β, un antagonista de la angiotensina II, un inhibidor de la enzima convertidora de angiotensina, un inhibidor de la aglutinación plaquetaria, un antagonista del receptor de fibrinógeno, aspirina, fentiraminas, agonistas del receptor adrenérgico β_3; sulfonilureas, biguanidas, inhibidores de α-glucosidasa, secretagogos de insulina, insulina y un agente hepatoprotector

31. Un método de conformidad con la reivindicación 27, caracterizado porque la enfermedad o condición es seleccionada del grupo que consiste de diabetes, obesidad y síndrome X.

32. Un método de conformidad con la reivindicación 27, caracterizado porque la enfermedad o condición es obesidad.

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33. Un método de conformidad con la reivindicación 27, caracterizado porque la enfermedad está asociada con DGAT.

34. Un método de conformidad con la reivindicación 27, caracterizado porque la enfermedad es mediada por DGAT.

35. Un método de conformidad con la reivindicación 27, caracterizado porque el compuesto interfiere con la interacción entre DGAT y un ligando.

36. Un método de conformidad con la reivindicación 27, caracterizado porque el sujeto es seleccionado del grupo que consiste de humano, rata, perro, vaca, caballo y ratón.

37. Un método de conformidad con la reivindicación 27, caracterizado porque el sujeto es humano.

38. Un método de conformidad con la reivindicación 27, caracterizado porque X es N.

39. Un método de conformidad con la reivindicación 38, caracterizado porque Z es O.

40. Un método de conformidad con la reivindicación 39, caracterizado porque L^1 es un enlace y W^1 es un elemento substituido o no substituido seleccionado del grupo que consiste de benceno, piridina, tiofeno, oxazol, tiazol, benzoxazol, benzotiazol, benzofurano, benzotiofeno, (C_4-C_7)-cicloalcano, (C_5-C_7)-cicloalqueno, 1,

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2, 3, 4-tetrahidronaftaleno e indano.

41. Un método de conformidad con la reivindicación 40, caracterizado porque W^1 es un elemento substituido o no substituido seleccionado del grupo que consiste de benceno, piridina, tiofeno, 1, 2, 3, 4-tetrahidronaftaleno e indano.

42. Un método de conformidad con la reivindicación 41, caracterizado porque el subíndice m es 1.

43. Un método de conformidad con la reivindicación 41, caracterizado porque el subíndice m es 1 y L^2 es un enlace.

44. Un compuesto de conformidad con la reivindicación 43, caracterizado porque W^2 es un elemento substituido o no substituido seleccionado del grupo que consiste de benceno, piridina, (C_4-C_7)-cicloalcano, (C_5-C_7)-cicloalqueno, pirrolidina, piperidina, piperazina y morfolina.

45. Un método de conformidad con la reivindicación 40, caracterizado porque R^5 y R^6 son seleccionados independientemente del grupo que consiste de H, (C_1-C_8)-alquilo, $C(O)R^a$ y CO_2R^a.

46. Un método de conformidad con la reivindicación 45, caracterizado porque R^5 y R^6 son seleccionados independientemente del grupo que consiste de H y (C_1-C_8)-alquilo.

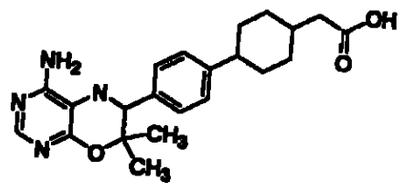
47. Un método de conformidad con la reivindicación 46, caracterizado porque R^3 y R^4 son seleccionados independientemente del grupo que consiste de H y (C_1-C_8)-alquilo.

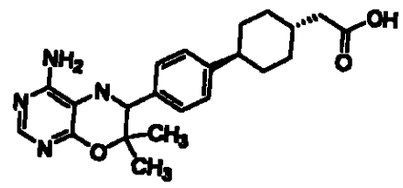
48. Un método de conformidad con la reivindicación 47, caracterizado porque R^7 es seleccionado del grupo que consiste de H, (C_1-C_8)-alquilo, halo-(C_1-C_4)-alquilo, OH y NR^aR^b en donde R^a y R^b son seleccionados independientemente del grupo que consiste de H y (C_1-C_8)-alquilo.

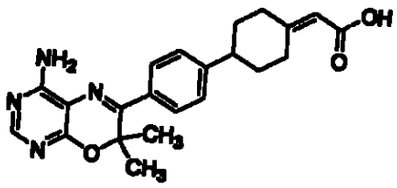
49. Un compuesto de conformidad con la reivindicación 47, caracterizado porque R^7 es H, (C_1-C_8)-alquilo o halo-(C_1-C_4)-alquilo.

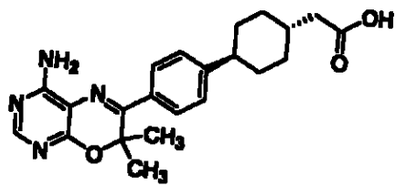
50. Un compuesto de conformidad con la reivindicación 1, caracterizado porque es seleccionado del grupo que consiste de

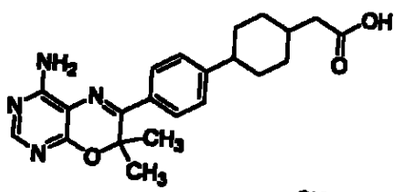
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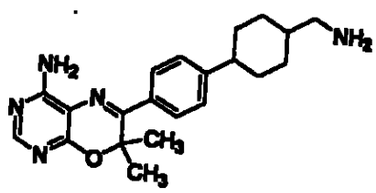


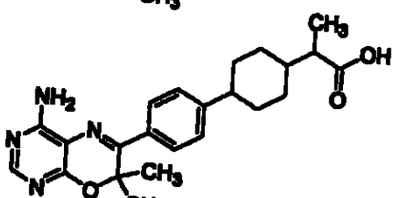


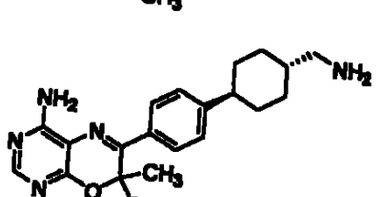


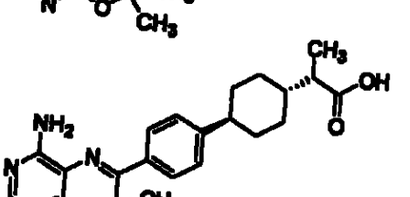


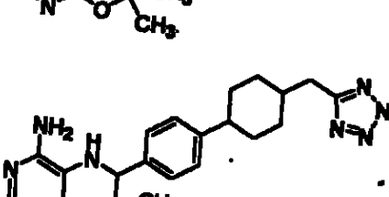


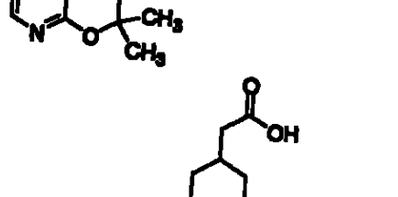


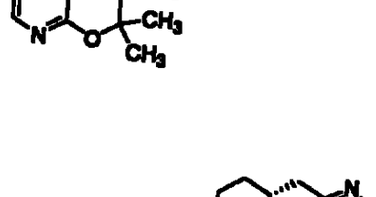


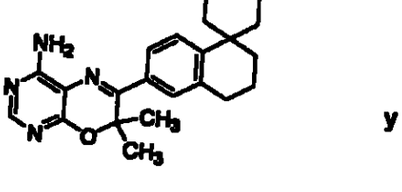


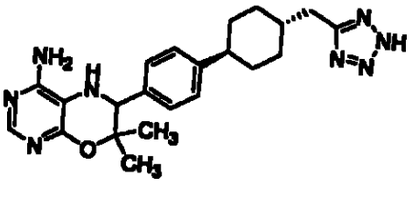


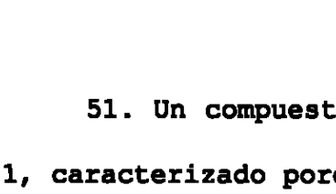








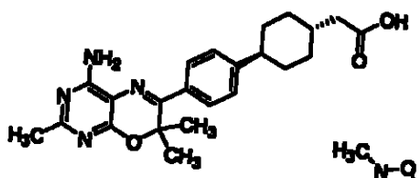


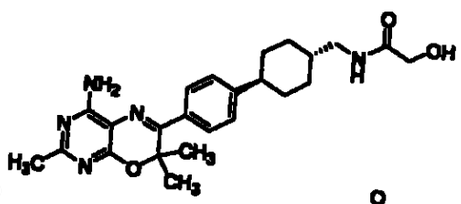


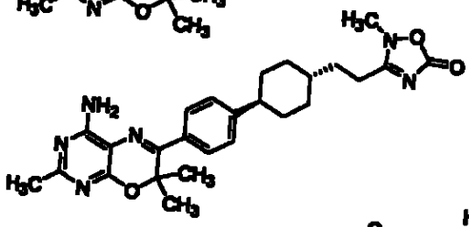
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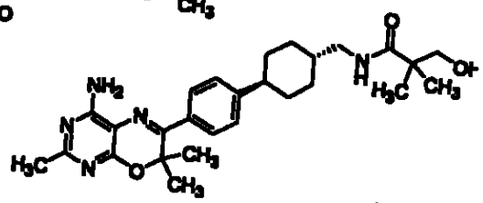
51. Un compuesto de conformidad con la reivindicación 1, caracterizado porque el grupo consiste de

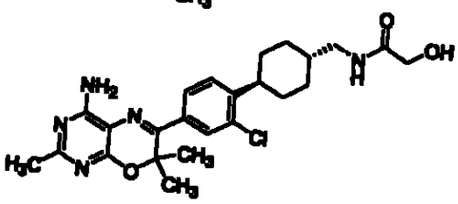
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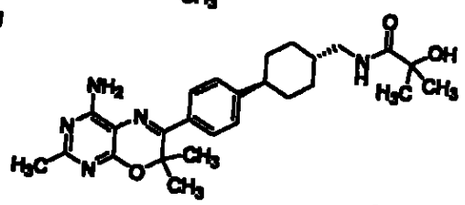


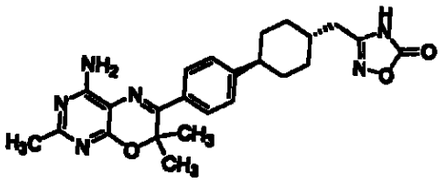


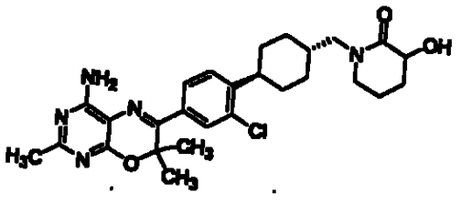


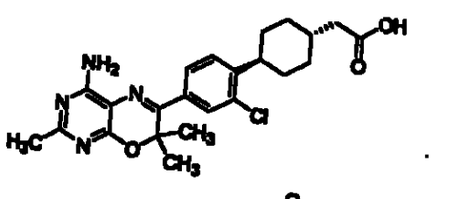


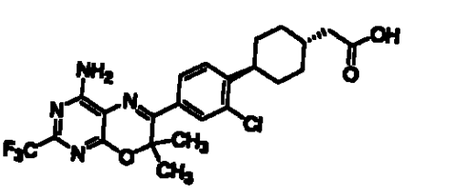


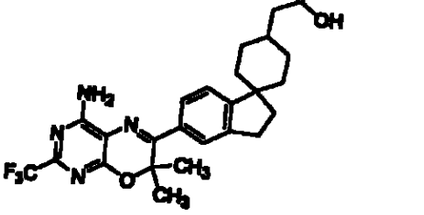


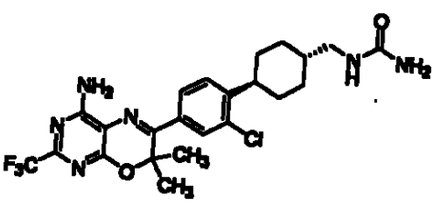


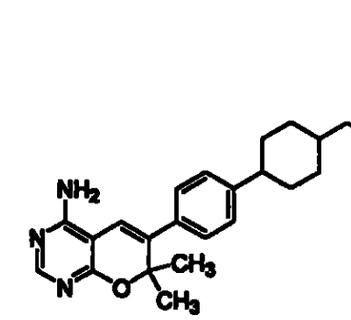


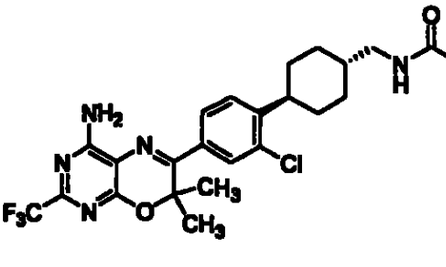




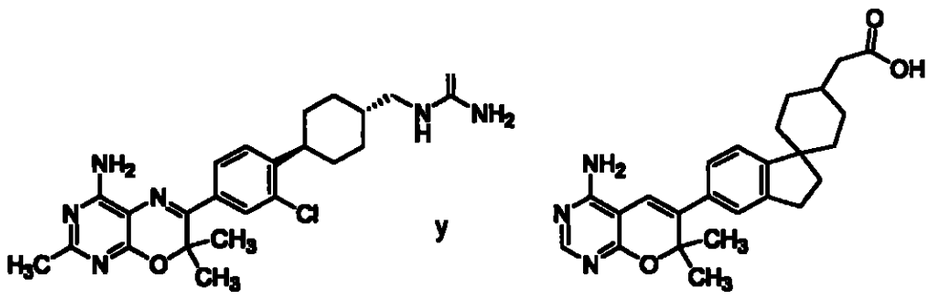








355



y

52. Un compuesto caracterizado porque tiene una fórmula seleccionada del grupo que consiste de Ia, Ib, Ic, Id, Ie, If y Ig.

53. Un compuesto caracterizado porque tiene una fórmula seleccionada del grupo que consiste de Ih, Ii, Ij y Ik.

54. Un compuesto caracterizado porque tiene una fórmula seleccionada del grupo que consiste de II, Im, In, Io, Ip y Iq.

55. Un compuesto caracterizado porque tiene una fórmula seleccionada del grupo que consiste de Ir, Is, Iť, Iu, Iv, Iw, Ix y Iy.

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RESUMEN DE LA INVENCION

Se proporcionan en la presente compuestos, composiciones y métodos que son útiles en el tratamiento o la prevención de enfermedades o condiciones metabólicas y de proliferación celular. En particular, la invención proporciona compuestos que modulan la actividad de las proteínas involucradas en el metabolismo lipídico y en la proliferación celular.

TOWNSEND & TOWNSEND AND CREW LLP
NOV 0 3 2004

WBK

TOWNSEND AND CREW LLP
NOV 0 3 2004

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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
WILLIAM B. KEZER
TOWNSEND AND TOWNSEND AND CREW LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

018781-009310PC

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing (day/month/year)	29 OCT 2004

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
18781-93-1PC	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US03/37574	21 November 2003 (21.11.2003)	22 November 2002 (22.11.2002)

Applicant

TULARIK, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

5/22/05

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450	Telephone No. (571) 272-1600
Facsimile No. (703) 305-3230	

Form PCT/IPEA/416 (July 1992)

Spec'd

UNDOCKETED BY

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 18781-93-1PC	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US03/37574	International filing date *(day/month/year)* 21 November 2003 (21.11.2003)	Priority date *(day/month/year)* 22 November 2002 (22.11.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): C07D 491/052, 498/04, 513/04; A61K 31/436, 31/4365 and US Cl.: 544/48, 105, 278, 114, 115; 514/222.8, 229.2, 258, 301, 302		
Applicant TULARIK, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of ___ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22 June 2004 (22.06.2004)	21 October 2004 (21.10.2004)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Venkataraman Balasubramanian Telephone No. (571) 272-1600

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/37574

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-162 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 163-175, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/37574

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	1-55	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	1-55	YES
	Claims	NONE	NO
Industrial Applicability (IA)	Claims	1-55	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-55 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the compound, composition and the method of use embraced in the claims 1-55.

Claims 1-55 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry as therapeutic agents to treat various diseases including obesity, diabetes and various cancers.

PATENT COOPERATION TREATY WBK

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From the INTERNATIONAL BUREAU

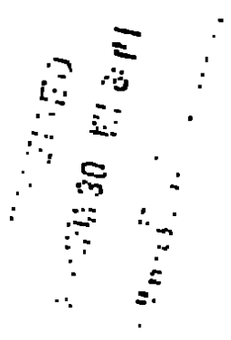
PCT

To:

018781-009310PC

KEZER, William, B.
Townsend and Townsend and Crew LLP
Two Embarcadero Center
Eighth Floor
San Francisco, CA 94111-3834
ETATS-UNIS D'AMERIQUE

DEC 0 3 2004



202

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 June 2004 (10.06.2004)

PCT

(10) International Publication Number
WO 2004/047755 A3

(51) International Patent Classification[7]: C07D 491/052, 498/04, 513/04, A61K 31/436, 31/4365

(21) International Application Number:
PCT/US2003/037574

(22) International Filing Date:
21 November 2003 (21.11.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/428,600 22 November 2002 (22.11.2002) US

(71) Applicants *(for all designated States except US)*: TULARIK INC. [US/US]; 1120 Veterans Boulevard, South San Francisco, CA 94080 (US). JAPAN TOBACCO, INC. [JP/JP]; 2-1, Toranomon 2-chome, Minato-ku, Tokyo 105-8422 (JP).

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(75) Inventors/Applicants *(for US only)*: FOX, Brian, M. [US/US]; 241 North El Camino Real, Apt. 101, San Mateo, CA 94401 (US). FURUKAWA, Noboru [JP/JP]; Japan Tobacco, Inc., Central Pharmaceutical Research Institute, 1-1 Murasaki-cho, Takatsuki, Osaka 569-1125 (JP). HAO, Xiaolin [CN/US]; 1200 East Hillsdale Blvd., Apt. 204, Foster City, CA 94404 (US). IIO, Kiyosei [JP/JP]; Japan Tobacco, Inc., Central Pharmaceutical Research Institute, 1-1 Murasaki-cho, Takatsuki, Osaka 569-1125 (JP). INABA, Takashi [JP/JP]; Japan Tobacco, Inc., Central Pharmaceutical Research Institute, 1-1 Murasaki-cho, Takatsuki, Osaka 569-1125 (JP). JACKSON, Simon, M. [GB/US]; 1950 Brittan Avenue, San Carlos, CA 94070 (US). KAYSER, Frank [DE/US]; 4150 17th Street, #25, San Francisco, CA 94114 (US). LABELLE, Marc [CA/US]; 2705 Mariposa Drive, Burlingame, CA 94010 (US). LI, Kexue [CN/US]; 3860 Park Blvd., #3B, Palo Alto, CA 94306 (US). MATSUI, Takuya [JP/JP]; Japan Tobacco, Inc., Central Pharmaceutical Research Institute, 1-1 Murasaki-cho, Takatsuki, Osaka 569-1125 (JP). MCMINN, Dustin, L. [US/US]; 1065 Grand Teton Drive, Pacifica, CA 94044 (US). OGAWA, Nobuya [JP/JP]; Japan Tobacco, Inc., Central Pharmaceutical Research Institute, 1-1 Murasaki-cho, Takatsuki, Osaka 569-1125 (JP). RUBENSTEIN, Steven, M. [US/US]; 1027 Anza Drive, Pacifica, CA 94044 (US). SAGAWA, Shoichi [JP/JP]; Japan Tobacco, Inc., Central Pharmaceutical Research Institute, 1-1 Murasaki-cho, Takatsuki, Osaka 569-1125 (JP). SUGIMOTO, Kazuyuki [JP/JP]; Japan Tobacco, Inc., Central Pharmaceutical Research Institute, 1-1 Murasaki-cho, Takatsuki, Osaka 569-1125 (JP). SUZUKI, Masahiro [JP/JP]; Japan Tobacco, Inc., Central Pharmaceutical Research Institute, 1-1 Murasaki-cho, Takatsuki, Osaka 569-1125 (JP). TANAKA, Masahiro [JP/JP]; Japan Tobacco, Inc., Central Pharmaceutical Research Institute, 1-1 Murasaki-cho, Takatsuki, Osaka 569-1125 (JP). YE, Guosen [CN/US]; 343 East High Street, Pheonixville, PA 19460 (US). YOSHIDA, Atsuhito [JP/JP]; Japan Tobacco, Inc., Central Pharmaceutical Research Institute, 1-1 Murasaki-cho, Takatsuki, Osaka 569-1125 (JP). ZHANG, Jian [CN/US]; 704 Nina Lane, Foster City, CA 94404 (US).

(74) Agents: KEZER, William, B. et al.; Townsend and Townsend and Crew LLP, Two Embarcadero Center, Eighth Floor, San Francisco, CA 94111-3834 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
25 November 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: FUSED BICYCLIC NITROGEN-CONTAINING HETEROCYCLES

(57) Abstract: Compounds, pharmaceutical compositions and methods that are useful in the treatment or prevention of metabolic and cell proliferative diseases or conditions are provided herein. In particular, the invention provides compounds which modulate the activity of proteins involved in lipid metabolism and cell proliferation.

WO 2004/047755 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/37574

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 491/052, 498/04, 513/04; A61K 31/436, 31/4365
US CL : 544/48, 105, 278, 114, 115; 514/222.8, 229.2, 258, 301, 302

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 544/48

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE, EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/32632 A2 (ELI LILLY AND COMPANY) 10 May 2001 (10.05.2001), see entire document.	1-55

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 June 2004 (29.06.2004)	14 SEP 2004
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Venkataraman Balasubramanian Telephone No. (703)308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

PCT REQUEST

18781-93-1PC

Original (for SUBMISSION) - printed on 21.11.2003 03:53:54 PM

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.11.2003)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	18781-93-1PC
I	Title of invention	FUSED BICYCLIC NITROGEN-CONTAINING HETEROCYCLES
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	TULARIK INC.
II-5	Address:	1120 Veterans Boulevard South San Francisco, CA 94080 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	650-825-7000
II-9	Facsimile No.	650-825-7392
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant only
III-1-2	Applicant for	all designated States except US
III-1-4	Name	JAPAN TOBACCO, INC.
III-1-5	Address:	2-1, Toranomon 2-chome Minato-ku, Tokyo 105-8422 Japan
III-1-6	State of nationality	JP
III-1-7	State of residence	JP

III-2	Applicant and/or Inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	FOX, Brian, M.
III-2-5	Address:	241 North El Camino Real, Apt. 101 San Mateo, CA 94401 United States of America
III-2-6	State of nationality	US
III-2-7	State of residence	US
III-3	Applicant and/or Inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	FURUKAWA, Noboru
III-3-5	Address:	Japan Tobacco, Inc. Central Pharmaceutical Research Institute 1-1 Murasaki-cho Takatsuki, Osaka 569-1125 Japan
III-3-6	State of nationality	JP
III-3-7	State of residence	JP
III-4	Applicant and/or Inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	HAO, Xiaolin
III-4-5	Address:	1200 East Hillsdale Blvd., Apt. 204 Foster City, CA 94404 United States of America
III-4-6	State of nationality	CN
III-4-7	State of residence	US
III-5	Applicant and/or Inventor	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	IIO, Kiyosei
III-5-5	Address:	Japan Tobacco, Inc. Central Pharmaceutical Research Institute 1-1 Murasaki-cho Takatsuki, Osaka 569-1125 Japan
III-5-6	State of nationality	JP
III-5-7	State of residence	JP

III-6	Applicant and/or Inventor	
III-6-1	This person is:	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	INABA, Takashi
III-6-5	Address:	Japan Tobacco, Inc. Central Pharmaceutical Research Institute 1-1 Murasaki-cho Takatsuki, Osaka 569-1125 Japan
III-6-6	State of nationality	JP
III-6-7	State of residence	JP
III-7	Applicant and/or Inventor	
III-7-1	This person is:	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	JACKSON, Simon, M.
III-7-5	Address:	1950 Brittan Avenue San Carlos, CA 94070 United States of America
III-7-6	State of nationality	GB
III-7-7	State of residence	US
III-8	Applicant and/or Inventor	
III-8-1	This person is:	applicant and inventor
III-8-2	Applicant for	US only
III-8-4	Name (LAST, First)	KAYSER, Frank
III-8-5	Address:	4150 17th Street, #25 San Francisco, CA 94114 United States of America
III-8-6	State of nationality	DE
III-8-7	State of residence	US
III-9	Applicant and/or Inventor	
III-9-1	This person is:	applicant and inventor
III-9-2	Applicant for	US only
III-9-4	Name (LAST, First)	LABELLE, Marc
III-9-5	Address:	2705 Mariposa Drive Burlingame, CA 94010 United States of America
III-9-6	State of nationality	CA
III-9-7	State of residence	US

III-10	Applicant and/or inventor	
III-10-1	This person is:	applicant and inventor
III-10-2	Applicant for	US only
III-10-4	Name (LAST, First)	LI, Kexue
III-10-5	Address:	3860 Park Blvd., #3B Palo Alto, CA 94306 United States of America
III-10-6	State of nationality	CN
III-10-7	State of residence	US
III-11	Applicant and/or inventor	
III-11-1	This person is:	applicant and inventor
III-11-2	Applicant for	US only
III-11-4	Name (LAST, First)	MATSUI, Takuya
III-11-5	Address:	Japan Tobacco, Inc. Central Pharmaceutical Research Institute 1-1 Murasaki-cho Takatsuki, Osaka 569-1125 Japan
III-11-6	State of nationality	JP
III-11-7	State of residence	JP
III-12	Applicant and/or inventor	
III-12-1	This person is:	applicant and inventor
III-12-2	Applicant for	US only
III-12-4	Name (LAST, First)	MCMINN, Dustin, L.
III-12-5	Address:	1065 Grand Teton Drive Pacifica, CA 94044 United States of America
III-12-6	State of nationality	US
III-12-7	State of residence	US
III-13	Applicant and/or inventor	
III-13-1	This person is:	applicant and inventor
III-13-2	Applicant for	US only
III-13-4	Name (LAST, First)	OGAWA, Nobuya
III-13-5	Address:	Japan Tobacco, Inc. Central Pharmaceutical Research Institute 1-1 Murasaki-cho Takatsuki, Osaka 569-1125 Japan
III-13-6	State of nationality	JP
III-13-7	State of residence	JP

III-14	Applicant and/or inventor	
III-14-1	This person is:	applicant and inventor
III-14-2	Applicant for	US only
III-14-4	Name (LAST, First)	RUBENSTEIN, Steven, M.
III-14-5	Address:	1027 Anza Drive Pacifica, CA 94044 United States of America
III-14-6	State of nationality	US
III-14-7	State of residence	US
III-15	Applicant and/or inventor	
III-15-1	This person is:	applicant and inventor
III-15-2	Applicant for	US only
III-15-4	Name (LAST, First)	SAGAWA, Shoichi
III-15-5	Address:	Japan Tobacco, Inc. Central Pharmaceutical Research Institute 1-1 Murasaki-cho Takatsuki, Osaka 569-1125 Japan
III-15-6	State of nationality	JP
III-15-7	State of residence	JP
III-16	Applicant and/or inventor	
III-16-1	This person is:	applicant and inventor
III-16-2	Applicant for	US only
III-16-4	Name (LAST, First)	SUGIMOTO, Kazuyuki
III-16-5	Address:	Japan Tobacco, Inc. Central Pharmaceutical Research Institute 1-1 Murasaki-cho Takatsuki, Osaka 569-1125 Japan
III-16-6	State of nationality	JP
III-16-7	State of residence	JP
III-17	Applicant and/or inventor	
III-17-1	This person is:	applicant and inventor
III-17-2	Applicant for	US only
III-17-4	Name (LAST, First)	SUZUKI, Masahiro
III-17-5	Address:	Japan Tobacco, Inc. Central Pharmaceutical Research Institute 1-1 Murasaki-cho Takatsuki, Osaka 569-1125 Japan
III-17-6	State of nationality	JP
III-17-7	State of residence	JP

III-18	Applicant and/or Inventor	
III-18-1	This person is:	applicant and inventor
III-18-2	Applicant for	US only
III-18-4	Name (LAST, First)	TANAKA, Masahiro
III-18-5	Address:	Japan Tobacco, Inc. Central Pharmaceutical Research Institute 1-1 Murasaki-cho Takatsuki, Osaka 569-1125 Japan
III-18-6	State of nationality	JP
III-18-7	State of residence	JP
III-19	Applicant and/or Inventor	
III-19-1	This person is:	applicant and inventor
III-19-2	Applicant for	US only
III-19-4	Name (LAST, First)	YE, Guosen
III-19-5	Address:	941 Hill Street, #210 Belmont, CA 94002 United States of America
III-19-6	State of nationality	CN
III-19-7	State of residence	US
III-20	Applicant and/or Inventor	
III-20-1	This person is:	applicant and inventor
III-20-2	Applicant for	US only
III-20-4	Name (LAST, First)	YOSHIDA, Atsuhito
III-20-5	Address:	Japan Tobacco, Inc. Central Pharmaceutical Research Institute 1-1 Murasaki-cho Takatsuki, Osaka 569-1125 Japan
III-20-6	State of nationality	JP
III-20-7	State of residence	JP
III-21	Applicant and/or Inventor	
III-21-1	This person is:	applicant and inventor
III-21-2	Applicant for	US only
III-21-4	Name (LAST, First)	ZHANG, Jian
III-21-5	Address:	704 Nina Lane Foster City, CA 94404 United States of America
III-21-6	State of nationality	CN
III-21-7	State of residence	US

IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	KEZER, William, B.
IV-1-2	Address:	Townsend and Townsend and Crew LLP Two Embarcadero Center Eighth Floor San Francisco, CA 94111-3834 United States of America
IV-1-3	Telephone No.	415-576-0200
IV-1-4	Facsimile No.	415-576-0300
IV-1-5	Agent's registration No.	37,369
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	GARRETT-WACKOWSKI, Eugenia; SNYDER, Joseph, R.; MYCROFT, Frank, J.; GRAY, Gerald, T.; KUSHA, Babak; LIEBESCHUETZ, Joe; PARENT, Annette, S.; MANN, Jeffry, S.; HINSCH, Matthew, E.; LOCKYER, Jean, M.; JENKINS, Kenneth, E.; SHAFFER, William, L.
IV-3	Additional agent(s)	agent
IV-3-1	Name (LAST, First)	SMITH, Christopher, J.
IV-3-2	Address:	Tularik Inc. 1120 Veterans Boulevard South San Francisco, CA 94080 United States of America
IV-3-3	Telephone No.	650-825-7000
IV-3-4	Facsimile No.	650-825-7392

V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: BW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	22 November 2002 (22.11.2002)
VI-1-2	Number	60/428,600
VI-1-3	Country	US

VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1	
VII-1	International Searching Authority Chosen	United States Patent and Trademark Office (USPTO) (ISA/US)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	1	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	

VIII-4-1	Declaration: Inventorship (only for the purposes of the designation of the United States of America) Declaration of inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:	I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought. This declaration is directed to the international application of which it forms a part (if filing declaration with application). I hereby declare that my residence, mailing address, and citizenship are as stated next to my name. I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications," by application number, country or Member of the World Trade Organization, day, month and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States f America, having a filing date before that of the application on which foreign priority is claimed.
VIII-4-1-1	Prior applications:	

		I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
VIII-4-1-1-1	Name:	FOX, Brian, M.
VIII-4-1-1-2	Residence: (city and either US State, if applicable, or country)	
VIII-4-1-1-3	Mailing address:	241 North El Camino Real, Apt. 101 San Mateo, CA 94401 United States of America
VIII-4-1-1-4	Citizenship:	US
VIII-4-1-1-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-1-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

VIII-4-1-2-1	Name:	FURUKAWA, Noboru
VIII-4-1-2-2	Residence: (city and either US State, if applicable, or country)	
VIII-4-1-2-3	Mailing address:	Japan Tobacco, Inc. Central Pharmaceutical Research Institute 1-1 Murasaki-cho Takatsuki, Osaka 569-1125 Japan
VIII-4-1-2-4	Citizenship:	JP
VIII-4-1-2-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-2-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1-3-1	Name:	HAO, Xiaolin
VIII-4-1-3-2	Residence: (city and either US State, if applicable, or country)	
VIII-4-1-3-3	Mailing address:	1200 East Hillsdale Blvd., Apt. 204 Foster City, CA 94404 United States of America
VIII-4-1-3-4	Citizenship:	CN
VIII-4-1-3-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-3-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

VIII-4-1-4-1	Name:	IIO, Kiyosei
VIII-4-1-4-2	Residence: (city and either US State, if applicable, or country)	
VIII-4-1-4-3	Mailing address:	Japan Tobacco, Inc. Central Pharmaceutical Research Institute 1-1 Murasaki-cho Takatsuki, Osaka 569-1125 Japan
VIII-4-1-4-4	Citizenship:	JP
VIII-4-1-4-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-4-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1-5-1	Name:	INABA, Takashi
VIII-4-1-5-2	Residence: (city and either US State, if applicable, or country)	
VIII-4-1-5-3	Mailing address:	Japan Tobacco, Inc. Central Pharmaceutical Research Institute 1-1 Murasaki-cho Takatsuki, Osaka 569-1125 Japan
VIII-4-1-5-4	Citizenship:	JP
VIII-4-1-5-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-5-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

VIII-4-1-6-1	Name:	JACKSON, Simon, M.
VIII-4-1-6-2	Residence: (city and either US State, if applicable, or country)	
VIII-4-1-6-3	Mailing address:	1950 Brittan Avenue San Carlos, CA 94070 United States of America
VIII-4-1-6-4	Citizenship:	GB
VIII-4-1-6-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-6-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1-7-1	Name:	KAYSER, Frank
VIII-4-1-7-2	Residence: (city and either US State, if applicable, or country)	
VIII-4-1-7-3	Mailing address:	4150 17th Street, #25 San Francisco, CA 94114 United States of America
VIII-4-1-7-4	Citizenship:	DE
VIII-4-1-7-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-7-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

VIII-4-1-8-1	Name:	LABELLE, Marc
VIII-4-1-8-2	Residence: (city and either US State, if applicable, or country)	
VIII-4-1-8-3	Mailing address:	2705 Mariposa Drive Burlingame, CA 94010 United States of America
VIII-4-1-8-4	Citizenship:	CA
VIII-4-1-8-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-8-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1-9-1	Name:	LI, Kexue
VIII-4-1-9-2	Residence: (city and either US State, if applicable, or country)	
VIII-4-1-9-3	Mailing address:	3860 Park Blvd., #3B Palo Alto, CA 94306 United States of America
VIII-4-1-9-4	Citizenship:	CN
VIII-4-1-9-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-9-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

VIII-4-1-10-1	Name:	MATSUI, Takuya
VIII-4-1-10-2	Residence: (city and either US State, if applicable, or country)	
VIII-4-1-10-3	Mailing address:	Japan Tobacco, Inc. Central Pharmaceutical Research Institute 1-1 Murasaki-cho Takatsuki, Osaka 569-1125 Japan
VIII-4-1-10-4	Citizenship:	JP
VIII-4-1-10-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-10-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1-11-1	Name:	MCMINN, Dustin, L.
VIII-4-1-11-2	Residence: (city and either US State, if applicable, or country)	
VIII-4-1-11-3	Mailing address:	1065 Grand Teton Drive Pacifica, CA 94044 United States of America
VIII-4-1-11-4	Citizenship:	US
VIII-4-1-11-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-11-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

VIII-4-1-12-1	Name:	OGAWA, Nobuya
VIII-4-1-12-2	Residence: (city and either US State, if applicable, or country)	
VIII-4-1-12-3	Mailing address:	Japan Tobacco, Inc. Central Pharmaceutical Research Institute 1-1 Murasaki-cho Takatsuki, Osaka 569-1125 Japan
VIII-4-1-12-4	Citizenship:	JP
VIII-4-1-12-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-12-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1-13-1	Name:	RUBENSTEIN, Steven, M.
VIII-4-1-13-2	Residence: (city and either US State, if applicable, or country)	
VIII-4-1-13-3	Mailing address:	1027 Anza Drive Pacifica, CA 94044 United States of America
VIII-4-1-13-4	Citizenship:	US
VIII-4-1-13-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-13-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

VIII-4-1-14-1	Name:	SAGAWA, Shoichi
VIII-4-1-14-2	Residence: (city and either US State, if applicable, or country)	
VIII-4-1-14-3	Mailing address:	Japan Tobacco, Inc. Central Pharmaceutical Research Institute 1-1 Murasaki-cho Takatsuki, Osaka 569-1125 Japan
VIII-4-1-14-4	Citizenship:	JP
VIII-4-1-14-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-14-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1-15-1	Name:	SUGIMOTO, Kazuyuki
VIII-4-1-15-2	Residence: (city and either US State, if applicable, or country)	
VIII-4-1-15-3	Mailing address:	Japan Tobacco, Inc. Central Pharmaceutical Research Institute 1-1 Murasaki-cho Takatsuki, Osaka 569-1125 Japan
VIII-4-1-15-4	Citizenship:	JP
VIII-4-1-15-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-15-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

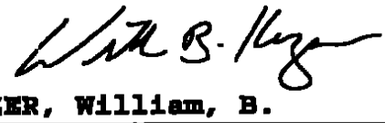
VIII-4-1-16-1	Name:	SUZUKI, Masahiro
VIII-4-1-16-2	Residence: (city and either US State, if applicable, or country)	
VIII-4-1-16-3	Mailing address:	Japan Tobacco, Inc. Central Pharmaceutical Research Institute 1-1 Murasaki-cho Takatsuki, Osaka 569-1125 Japan
VIII-4-1-16-4	Citizenship:	JP
VIII-4-1-16-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-16-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1-17-1	Name:	TANAKA, Masahiro
VIII-4-1-17-2	Residence: (city and either US State, if applicable, or country)	
VIII-4-1-17-3	Mailing address:	Japan Tobacco, Inc. Central Pharmaceutical Research Institute 1-1 Murasaki-cho Takatsuki, Osaka 569-1125 Japan
VIII-4-1-17-4	Citizenship:	JP
VIII-4-1-17-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-17-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

VIII-4-1-18-1	Name:	YE, Guosen
VIII-4-1-18-2	Residence: (city and either US State, if applicable, or country)	
VIII-4-1-18-3	Mailing address:	941 Hill Street, #210 Belmont, CA 94002 United States of America
VIII-4-1-18-4	Citizenship:	CN
VIII-4-1-18-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-18-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1-19-1	Name:	YOSHIDA, Atsuhito
VIII-4-1-19-2	Residence: (city and either US State, if applicable, or country)	
VIII-4-1-19-3	Mailing address:	Japan Tobacco, Inc. Central Pharmaceutical Research Institute 1-1 Murasaki-cho Takatsuki, Osaka 569-1125 Japan
VIII-4-1-19-4	Citizenship:	JP
VIII-4-1-19-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-19-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

VIII-4-1 -20-1	Name:	ZHANG, Jian
VIII-4-1 -20-2	Residence: (city and either US State, if applicable, or country)	
VIII-4-1 -20-3	Mailing address:	704 Nina Lane Foster City, CA 94404 United States of America
VIII-4-1 -20-4	Citizenship:	CN
VIII-4-1 -20-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1 -20-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

PCT REQUEST 18781-93-1PC

Original (for SUBMISSION) - printed on 21.11.2003 03:53:54 PM

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	24	-
IX-2	Description	162	-
IX-3	Claims	13	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	200	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-11	Copy of general power of attorney	reference no. 018781-009310PC	-
IX-17	PCT-EASY diskette	-	Diskette
IX-18	Other (specified):	Postcard	-
IX-18	Other (specified):	Transmittal Letter	-
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST, First)	KEZER, William, B.	
X-2	Signature of applicant, agent or common representative		
X-2-1	Name	JAPAN TOBACCO, INC.	
X-2-2	Name of signatory	Teruo Daito	
X-2-3	Capacity	Director of Intellectual Property	
X-3	Signature of applicant, agent or common representative		
X-3-1	Name (LAST, First)	FOX, Brian, M.	
X-4	Signature of applicant, agent or common representative		
X-4-1	Name (LAST, First)	FURUKAWA, Noboru	
X-5	Signature of applicant, agent or common representative		
X-5-1	Name (LAST, First)	HAO, Xiaolin	
X-6	Signature of applicant, agent or common representative		
X-6-1	Name (LAST, First)	IIO, Kiyosei	

X-7	Signature of applicant, agent or common representative	
X-7-1	Name (LAST, First)	INABA, Takashi
X-8	Signature of applicant, agent or common representative	
X-8-1	Name (LAST, First)	JACKSON, Simon, M.
X-9	Signature of applicant, agent or common representative	
X-9-1	Name (LAST, First)	KAYSER, Frank
X-10	Signature of applicant, agent or common representative	
X-10-1	Name (LAST, First)	LABELLE, Marc
X-11	Signature of applicant, agent or common representative	
X-11-1	Name (LAST, First)	LI, Kexue
X-12	Signature of applicant, agent or common representative	
X-12-1	Name (LAST, First)	MATSUI, Takuya
X-13	Signature of applicant, agent or common representative	
X-13-1	Name (LAST, First)	MCMINN, Dustin, L.
X-14	Signature of applicant, agent or common representative	
X-14-1	Name (LAST, First)	OGAWA, Nobuya
X-15	Signature of applicant, agent or common representative	
X-15-1	Name (LAST, First)	RUBENSTEIN, Steven, M.
X-16	Signature of applicant, agent or common representative	
X-16-1	Name (LAST, First)	SAGAWA, Shoichi
X-17	Signature of applicant, agent or common representative	
X-17-1	Name (LAST, First)	SUGIMOTO, Kazuyuki

X-18	Signature of applicant, agent or common representative	
X-18-1	Name (LAST, First)	SUZUKI, Masahiro
X-19	Signature of applicant, agent or common representative	
X-19-1	Name (LAST, First)	TANAKA, Masahiro
X-20	Signature of applicant, agent or common representative	
X-20-1	Name (LAST, First)	YE, Guosen
X-21	Signature of applicant, agent or common representative	
X-21-1	Name (LAST, First)	YOSHIDA, Atsuhito
X-22	Signature of applicant, agent or common representative	
X-22-1	Name (LAST, First)	ZHANG, Jian

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10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/US
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

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REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN MODELO DE UTILIDAD	( )	( )
- Indicación de que se solicita la concesión de una patente.	( )	( )
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
Descripción de la Invención.	( )	( )
Dibujos de ser estos pertinentes.	( )	( )
Comprobante de Pago de las tasas establecidas.		
COMPLETA ( ) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable:

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05049678 00000000 Folios: 387
Fecha (AMD): 2005-05-23 16:46:29
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAN
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCI

Bogotá,
2020

389

Doctor(a)
RODRIGUEZ D'ALEMAN DILIA MARIA

REFERENCIA	Radicación No.	5 49678
	Solicitud internacional	US2003/037574
	Fecha inicio fase nacional	22/06/2005
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	06573

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. Si fuere el caso, el solicitante debe adjuntar la traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT).

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

3. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

Continua en la página siguiente...

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REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

390

Radicación No.:5 49678

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la divisiin de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 05 AGO. 2005
adpal